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Interdisciplinary expert team statement on the treatment of multi-bed atherosclerotic disease — endorsed by Polish Cardiac Society, Polish Lipid Association, Polish Society of Diabetology, Polish Neurological Society, Polish Society of Nephrology

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ABSTRACT

Atherosclerosis is a systemic disease and involves not only the coronary vessels but also occurs in other vascular beds (e.g., cervical, cerebral, and peripheral vessels), increasing cardiovascular risk. One of the causes of atherosclerosis is lipid disorders. In addition, other diseases, such as diabetes, chronic kidney disease, or familial hypercholesterolemia, accelerate the development of multi-bed (multilevel) atherosclerosis. So far, such patients are often treated by physicians of various specialties, and in our country, there is no integrated system for managing these patients and their further treatment. This frequently results in the inability to achieve the therapeutic goals for low-density lipoprotein cholesterol set by the guidelines despite the availability of modern therapy for the treatment of lipid disorders in our country.

The presented expert position paper postulates modification of the treatment of patients with multi-bed atherosclerosis by strengthening cooperation between physicians of many specialties (cardiologists, diabetologists, nephrologists, vascular surgeons, pediatricians, etc.) in order to improve the effectiveness of treatment and better educate the medical community and the treated patients.

Key words: interdisciplinary management, LDL cholesterol, multi-bed atherosclerosis

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AS AN INTERDISCIPLINARY PROBLEM

According to World Health Organization data [1], Poland, in contrast to the Western countries of the European Union, is considered to have high cardiovascular (CV) risk. The new Global Burden of Disease 2023 report shows that death rates and disability-adjusted life years are up

to three times higher than in Western European and Scandinavian countries [2]. According to the guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), the group of high- and very high-risk patients includes patients with cardiovascular diseases (patients after myocardial infarction, with the chronic coronary syndrome, subjects after stroke or transient ischemic attack (TIA), atherosclerotic peripheral arterial diseases of either lower limbs or carotid arteries, patients after revascularization of the peripheral arteries, as well as with an aortic aneurysm), patients with diabetes mellitus, familial hypercholesterolemia (FH), severe hypercholesterolemia or severe hypertension, arterial disease, chronic kidney disease (CKD) or high and very high risk as determined by the SCORE2/SCORE2-OP risk scores [1, 3].

The 2021 Polish guidelines for the treatment of lipid disorders (PTL/KLRWP/PTK/PTDL/PTD/PTNT) distinguish an additional patient population among patients at very high cardiovascular risk — the extreme cardiovascular risk group [4]. This subgroup of patients includes those with a history of the acute coronary syndrome (ACS) and another vascular incident within the past 2 years, subjects after ACS with either peripheral vascular disease or multilevel atherosclerosis, patient after ACS with concomitant multivessel coronary disease, after ACS and with FH, and post-ACS patients with concomitant diabetes and at least one additional risk factor — elevated lipoprotein a >50 mg/dl (>125 nmol/l) or high-sensitivity C-reactive protein >3 mg/l or chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2), as well as patients in the primary prevention with Pol-SCORE risk of >20% (SCORE2 >25%) [5].

In Poland, even more than 21 million of the population have hypercholesterolemia [6], and it is estimated that 140 000 patients have familial hypercholesterolemia [4]. More than 80 000 patients develop myocardial infarction each year [7], and more than 74 000 patients develop an ischemic stroke [8].

A key role in the atherosclerotic process, apart from inflammation, is played by elevated cholesterol levels. It has been documented that the higher the concentration of total cholesterol and low-density lipoprotein cholesterol (LDL-C), the higher the risk of atherosclerosis and related complications, both within the coronary vessels as well as in the other vascular systems [3]. High concentration of LDL-C contributes to the formation of atherosclerotic plaque, which, increasing its volume and degenerating, leads to cardiovascular incidents once the thrombotic process cascade is eventually activated. Higher LDL-C concentrations in the blood might result in premature atherosclerotic plaque growth (e.g., already at a young age), which might exert an earlier occurrence of acute coronary syndromes. It has been proven that the sooner the initiation

of therapy and the lower the LDL-C concentrations achieved after therapy, the lower the risk of acute coronary syndromes in the future [4]. Therefore, we currently follow the principles of "the lower, the better for longer" and "the earlier (to reach the therapeutic goal), the better" when treating patients with lipid disorders [9].

Poland and other central and eastern European countries (except Slovenia) are still among the high cardiovascular-risk countries [1]. Of the group of these countries, only Slovenia is a country with a well-functioning cardiovascular prevention. The introduction of coordinated primary prevention care in patients in this country in the 1990s translated into a 50% reduction in the risk of all-cause and cardiovascular deaths [1]. In Poland, care is focused on treating patients who have already suffered a myocardial infarction, stroke, developed heart failure, or cancer, and comprehensive primary prevention schemes have not been initiated yet.

The Global Burden of Cardiovascular Diseases and Risks study assessed the impact of LDL-C levels on mortality rates associated with cardiovascular disease, living with disability, or years of life lost between 1990 and 2020 [2]. Analysis of age-standardized results demonstrated a slight decrease in mortality over the years. However, non-standardized data indicate a slight increase in mortality in all groups in recent years.

In 2022, out of 458 000 deaths in Poland, approximately 160 000 were related to cardiovascular disease. Based on the Global Burden of Cardiovascular Diseases and Risks analysis, it can be assumed that approximately 8%–10% of all deaths were related to inadequate treatment of elevated LDL-C [2]. The same study indicates that abnormal LDL-C is responsible for up to 4.5 million cardiovascular deaths per year, corresponding to more than 30 000 deaths per year in Poland alone [2].

According to ESC guidelines, in very high-risk patients, the therapeutic goal for LDL-C is a reduction of at least 50% from baseline and an LDL-C goal concentration of less than 55 mg/dl (1.4 mmol/l). In contrast, in high-risk patients, it is a reduction of at least 50% from baseline and an LDL-C goal concentration of less than 70 mg/dl (1.8 mmol/l) [3]. In the extreme cardiovascular risk group, defined in these guidelines as the occurrence of at least two vascular incidents in the most recent years, the therapeutic goal is an LDL-C concentration below 40 mg/dL (1.0 mmol/l) [4].

A number of pharmacological modalities are used in the treatment of lipid disorders, which differ in their hypolipemic potency and effect on different lipidogram components. Statins are the cornerstone of therapy for lipid disorders and, if ineffective in monotherapy, should be used in combination with ezetimibe. In patients in whom this treatment is ineffective,

guidelines recommend adding proprotein type 9 subtilisin/kexin convertase (PCSK9) inhibitors or inclisiran to therapy [3, 4].

Unfortunately, the Polish and European reality falls far short of the therapeutic goals set by the ESC guidelines. In the Da Vinci study, only 24% of patients in Poland, irrespective of cardiovascular risk, achieved the therapeutic goal for LDL-C, and only 17% of patients in the very high-risk group achieved the goal of <55 mg/dl (1.4 mmol/l) and approximately 8% the goal for extreme risk [10]. In the group of very high-risk patients in whom the laboratory results are available, i.e., the group of post-MI patients participating in the Managed Care in Acute Myocardial Infarction (MACAMIS [Kos-Zawał]) program, the mean LDL-C concentration on admission was approximately 115.0 mg/dl (3.0 mmol/l). At the same time, after 12 months of therapy, it had fallen to 75.0 mg/dl (1.9 mmol/l) [11]. It was observed that more patients received immediate combination therapy (as recommended by the International Lipid Expert Panel in 2021 [12] and the latest ESC 2023 guidelines [13]). Moreover, the goal of <55 mg/dl (1.4 mmol/l) was reached by more than 20% of patients. On the other hand, it has been observed that one in four physicians reduced the statin dose when adding ezetimibe, which significantly reduced the percentage of patients in the therapeutic goal [11]. In the POLASPIRE study, it was found that only 38% of patients achieved LDL-C levels <70 mg/dl (<1.8 mmol/l) after ACS. Among these patients, only 16% achieved a therapeutic goal of <55 mg/dl (<1.4 mmol/l) [14].

Observations of patients followed up after hospital discharge in the KOS-Zawał program further show that combined therapy with a statin and ezetimibe affects a small proportion of patients (2.6% immediately after discharge and 20.8% one year after discharge). Furthermore, as mentioned above, the inclusion of ezetimibe is often associated with a reduction in the patient's statin dose. Even with high statin doses, a therapeutic goal of less than 55 mg/dl (1.4 mmol/l) is only achieved by about 20% of patients, with a further 20% of patients achieving a goal of 55-70 mg/dl (1.4–1.8 mmol/l) [11]. Unfortunately, at present, we do not have treatment results for other groups of very high-risk patients, but given data from other countries, the proportion of very high-risk patients achieving the ESC/EAS therapeutic goal may be even lower [15].

Factors limiting the effectiveness of treatment of hypercholesterolemia are: lack of lifestyle changes by patients, physicians' inertia and reluctance to administer high doses of statins or combined treatment, thus resulting in too low doses of drugs and/or lack of combined treatment (therapeutic inertia), as well as patients’ non-compliance to medical recommendations (non-adherence or irregular use of drugs). An optimally-designed continuous education for both doctors and other groups in the health care system (e.g., certification by the

Polish Lipid Society, EAS, etc.), as well as education of patients, are crucial to improving patients' outcomes. Inclusion of additional information in the hospital discharge note on what the goal LDL-C levels should be, what doses of statins the patient should take, and what steps should be taken if statin treatment fails (introduction of ezetimibe or, in exceptional cases, of a PCSK9 inhibitor or inclisiran) could also be helpful for both patients and general practitioners. An example of such a statement is the proposal prepared by the experts of the Polish Cardiac Society and Polish Lipid Association and published in the "Polish Heart Journal" [16].

An important issue of effective patient management is the selection of an appropriate statin and its appropriate dose, as well as the use of combined therapy with ezetimibe, also as the currently recommended immediate combination therapy, and only in the second or only in the third step with PCSK9 protein inhibitors or inclisiran. The only exception to this rule is the confirmed intolerance of statins and/or ezetimibe [3, 4].

It is worth mentioning that the identification of atherosclerosis in one vascular bed does not dispense clinicians from the necessity of looking for atherosclerosis in other areas. Data from the REACH registry indicate that 24.7% of patients with ischemic heart disease (CVD) had comorbidity in other vascular beds [17]. In 40.2% of patients with cerebrovascular disease, disease in other arterial beds coexisted, while 61.5% of patients with CVD had signs of atherosclerosis in other vascular beds (either carotid or coronary), which is called multi-bed atherosclerotic disease.

The analysis of long-term outcomes demonstrates that the development of atherosclerosis results in the occurrence of subsequent adverse cardiac events in up to 9% of patients per year if modern secondary prevention methods are not implemented [18]. Therefore, a multidisciplinary assessment of patients with atherosclerosis is necessary, as the disease should be considered a progressive, systemic condition and not limited to a single (e.g., coronary or cerebrovascular) vascular bed.

Diabetes mellitus as an interdisciplinary problem

Type 2 diabetes is a metabolic disorder in which increased blood glucose levels are often also accompanied by elevated blood pressure, lipid disorders, obesity, or overweight (the latter observed in 80% of patients). According to the ESC definition, a very high-risk patient is a patient with diabetes, known cardiovascular disease, and/or severe organ complications (these complications include chronic kidney disease with eGFR <45 ml/min/1.73 m^2 regardless of albuminuria, or with eGFR 45–59 ml/min/1.73 m^2 and with albuminuria (urine albumin/creatinine ratio — UACR 30–300 mg/g), or with proteinuria (UACR >300 mg/g), the

presence of microvascular disease in at least three locations such as albuminuria with retinopathy and neuropathy) [1, 3]. In comparison, in the recommendations on diabetes, the concept of very high risk in patients with type 2 diabetes is broader. It includes, in addition to comorbid atherosclerotic vascular disease with severe organ damage, a 10-year cardiovascular risk of >20% according to the SCORE2-Diabetes calculator [19, 20]. It is worth noting here that the SCORE2-Diabetes score could be considered controversial, as it allows patients with diabetes to appear as low- or moderate-risk and such patients are very rarely observed in practice. Such presentation may ultimately (considering only the variables included in the score) underestimate the risk and thus lead to insufficiently intensive preventive treatment [21, 22].

According to the TERCET registry [23], which includes more than 19 000 patients with non-ischemic heart disease, one-third of patients have comorbid diabetes. Data from the TERCET registry also indicate that the presence of diabetes doubles the risk of adverse cardiovascular events regardless of the presence of other risk factors [23]. These findings confirm the importance of multidisciplinary management.

The 2023 ESC guidelines for the management of patients with CVD and diabetes [19] maintained the earlier goal of LDL-C concentrations in very high- and high-risk patients as the 2019 guideline, which is also in line with the Polish Diabetological Society guidelines [24]. Interestingly, comparative analyses demonstrate that patients with diabetes after ACS have lower baseline LDL-C concentrations than patients without diabetes after ACS. This is likely caused by the introduction of earlier and more potent therapy aimed concomitantly at multiple risk factors in this patient group. Moreover, the prevalence of cardiovascular events is higher in patients with diabetes despite a lower prevalence of cardiovascular risk factors other than diabetes. The pharmacological strategies in patients with diabetes most often include stabilization of glycemia but, at the same time, normalization of blood pressure and lipid parameters with earlier incorporation of hypolipemic treatment and weight reduction [24].

Ischemic stroke/transient ischemic attack as an interdisciplinary problem

Similar to patients with ischemic heart disease, patients after ischemic stroke or TIA are at very high risk of atherosclerotic cardiovascular disease (ASCVD) and, in particular, recurrent ischemic stroke. Data from the TERCET registry indicate, that in more than 5% of patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) and 2% of patients with ST-segment elevation myocardial infarction there is a history of stroke. The lower stroke rate in the ST-segment elevation myocardial infarction group may be due to the younger age of

these patients. Secondary prevention with statins reduces the risk of subsequent stroke (by 12% for each mmol/l reduction in LDL-C concentration), as well as MI and death from vascular causes [25].

European Stroke Organization guidelines recommend treatment with high-dose atorvastatin (80 mg) in post-stroke patients to achieve goal LDL-C concentrations. A therapeutic goal has been set at below 70 mg/dl (<1.8 mmol/l), and in patients who cannot achieve this goal, combined therapy, i.e., the addition of ezetimibe or PCSK9 inhibitors to statins, may be used [26]. The same therapeutic goal is also found in the American Heart Association/American Stroke Association guidelines for the prevention of atherosclerotic stroke [27].

These recommendations differ significantly from the cardiology and Polish lipid disorders guidelines of 6 scientific societies [4] in terms of the therapeutic goal and from the Polish neurology guidelines. All Polish mentioned guidelines recommend a therapeutic LDL-C goal of <55 mg/dl (<1.4 mmol/l) in patients after atherosclerotic ischemic stroke or TIA [25]. There is a need here for interdisciplinary collaboration and joint guidelines with neurologists (to be established in 2025), as such inconsistent approaches to hypolipemic treatment goals for patients after ischemic stroke lead to only about 60% of the population in Poland (according to the LIPIDOGRAM study) being treated, and with a very low percentage of those achieving the therapeutic goal for patients at very high cardiovascular risk (<55 mg/dl/1.4 mmol/l) [28].

Importantly, it is not only high-dose statins that are relevant in the treatment of post-stroke patients. According to sub-analyses of the FOURIER and ODYSSEY OUTCOMES trials, PCSK9 inhibitors have an impact on reducing stroke incidence. In the FOURIER study, the use of evolocumab [29] reduced the incidence of repeat strokes, including ischemic stroke and combined ischemic stroke and TIA. The use of alirocumab in the ODYSSEY OUTCOMES trial led to a reduction in the incidence of stroke, including ischemic stroke, without affecting the incidence of hemorrhagic stroke [30]. This aspect also not infrequently results in post-stroke patients not receiving adequately intensive hypolipemic treatment. It should be emphasized here that a causal relationship between the use of statins and between low and very low LDL-C levels and the risk of hemorrhagic stroke has not been confirmed [31].

Peripheral arteriosclerosis as a multidisciplinary problem

Almost two-thirds of patients with peripheral arteriosclerosis (PAD) have atherosclerosis in any other vascular bed. Data from the TERCET registry show that PAD coexists in 11.2% of patients with ischemic heart disease [23]. In these patients, to reduce the risk of ASCVD-related

events, the 2019 ESC guidelines recommend hypolipemic treatment, including statins at the highest tolerated dose combined with ezetimibe and, if required, in combination with a PCSK9 inhibitor [3, 4]. Any reduction in LDL cholesterol levels lowers the risk of ischemic CV events and reduces the severity of symptoms of PAD while also increasing the patient's gait and walking distance. A systematic review of 18 clinical trials involving 10 000 patients with normal or elevated cholesterol concentrations found that hypolipemic treatment was associated with a 20% reduction in the overall incidence of CV events and a 14% reduction in all-cause mortality [32]. There is also evidence to suggest a benefit of lowering LDL-C levels in patients with carotid artery disease. A meta-analysis of randomized clinical trials involving >190 000 participants found that statin treatment in these patients was associated with a 21% reduction in the incidence of all types of stroke in different populations, and this effect depended mainly on the degree of LDL-C reduction [33].

According to the 2017 ESC Guidelines for the Diagnosis and Treatment of Peripheral Artery Disease for Patients with Peripheral Artery Disease, lowering LDL cholesterol to <70 mg/dl (<1.8 mmol/l) is optimally recommended [34]; however, results from recent studies and the Polish guidelines of 6 major scientific societies from 2021 recommend lowering the LDL-C levels to <55 mg/dl (<1.4 mmol/l), similar to carotid or vertebrobasilar atherosclerosis [4, 35]. In the subanalysis of patients from the MACAMIS (KOS-Zawał) program, similarly to patients with diabetes, subjects with myocardial infarction and concomitant PAD had mean LDL-C concentrations lower by approximately 20 mg/dl (0.5 mmol/l), while achieved mean LDL cholesterol concentrations were approximately 70 mg/dl (<1.8 mmol/l) [36].

In the ESC/EAS guidelines, the use of statins in patients with PAD for the secondary prevention of stroke, myocardial infarction, and other cardiovascular events received a class I recommendation. If the therapeutic goal is not achieved with statins, ezetimibe therapy might also be considered, and PCSK9 inhibitors may be used for patients who are statin intolerant or who fail to reach the therapeutic goal during treatment with statins or statins with ezetimibe [3].

PCSK9 inhibitors reduce the incidence of peripheral vascular events. Results from sub-analyses of the FOURIER and ODYSSEY OUTCOMES trials suggest that the use of PCSK9 inhibitors in patients with peripheral atherosclerosis is associated with a significant reduction in the incidence of CV events, including those associated with acute lower limb ischemia [37]. The use of PCSK9 inhibitors is associated with more significant absolute benefits in terms of reduction in major adverse cardiac events (MACE) in patients with atherosclerosis in multiple vascular beds compared with patients with atherosclerosis in a single vascular bed. Patients in the alirocumab-treated group with single- and triple-level disease had a relative risk of MACE

of 15% (HR, 0.85; 95% CI, 0.77–0.93) and 36% (HR, 0.64; 95% CI, 0.35–1.12), respectively [34]. These results demonstrate that with more progressed atherosclerosis, more potent drugs have a significantly greater potential to lower LDL-C levels and, thus, to reduce the relative risk of MACE more pronouncedly.

Familial hypercholesterolemia as an interdisciplinary problem

Another group of very high- and high-risk patients is those with FH. The prevalence of the disease in the Polish population is estimated to be approximately 4‰ [38]. According to the TERCET registry, patients with an ACS and definite FH were younger than those with probable FH (mean age 51 ± 8 years vs. 54 ± 8 years) [39]. Of these patients, 70% had a prior myocardial infarction, approximately 60%–70% of patients underwent revascularization (angioplasty or coronary artery bypass grafting), in addition, one in four patients had diabetes, one-third of patients had a family history of premature atherosclerosis, and approximately 7%–12% of patients had renal dysfunction (eGFR of less than 60 ml/min/1.73 m^2).

FH is diagnosed and treated too late in the Polish population. An analysis from the large Gdansk center showed that only 9% of patients under 40 years of age with FH have a diagnosed atherosclerotic cardiovascular disease. In contrast, patients over 40 years of age are almost 45% of the total number of such patients [40]. Recent data from the Lodz Center suggest that the mean age of diagnosis of patients with FH is still above 45 years (45.8 ± 14.9 years). Despite almost 50% having statin combination therapy with ezetimibe and one in four patients having PCSK9 inhibitor/inclisiran treatment, the therapeutic goal (<55 mg/dl) is achieved in only 39% of patients, including almost 60% on triple therapy (which increases the chance of being in the therapeutic goal by 4.5-fold) [41].

For this reason, nationwide prevention programs related to early diagnosis and primary prevention are critical. In the group of patients with FH and coexisting cardiovascular disease (very high-risk patients), the therapeutic goal for LDL cholesterol levels is below 55 mg/dl (1.4 mmol/l), while in the group of patients with FH without cardiovascular disease (high-risk), it is below 70 mg/dl (1.8 mmol/l) [3, 4].

Chronic kidney disease as an interdisciplinary problem

According to the ESC definition, patients with known cardiac disease and chronic kidney disease with an eGFR of 30–59 ml/min/1.73 m^2 are classified as high-risk patients and those with an eGFR <30 ml/min/1.73 m^2 are classified as very high-risk cardiovascular patients [1, 3]. This group of patients is heterogeneous and, therefore, extremely difficult to diagnose and

treat. CKD is diagnosed in up to 16% of the Polish population [42]. Atherosclerosis in patients with CKD is often not parallel to the classic form and mechanism of atherosclerosis seen in the general population, also due to the high calcification of plaques and increased inflammation. The cause of atherosclerosis in patients with kidney disease is either low HDL cholesterol (HDL-C) or dysfunctional HDL-C, which is often missed by standard investigations [43].

In patients with low GFR values, the atherosclerotic plaque undergoes sclerosis and calcification that involves the entire vessel wall, which is confirmed by the observations of both cardiac surgeons and invasive cardiologists. The early introduction of hypolipemic drugs as a part of primary prevention in people in the early stages of chronic kidney disease development could probably prevent the growth of rapidly progressive vascular changes — due to the inability to reduce the lipid core of calcified plaque — while it is probably less relevant for secondary prevention in patients with already developed chronic kidney disease [44].

The risk of cardiovascular disease, as well as the risk of progression of CKD, is estimated to be similar in patients with an eGFR of 60 ml/min/1.73 m^2 and concomitant significant albuminuria as in patients with an eGFR of 30 ml/min/1.73 m^2 without albuminuria. Albuminuria, as well as a vascular event in any of the vascular beds, is a manifestation of organ damage. Interestingly, the available evidence indicates that in patients with end-stage CKD requiring dialyzes, lowering LDL-C concentrations is not of similar importance in terms of reducing cardiovascular incidents [45]. According to nephrology guidelines, a statin (usually atorvastatin 40 or 80 mg) is recommended in combination with ezetimibe, but patients with CKD rarely receive statins at the highest doses [46]. In contrast, the therapeutic goal for LDL-C levels according to ESC recommendations, similar to the Polish guidelines, is identical to that for other high and very-high cardiovascular-risk patients [3, 4].

Current Polish model of modern treatment of atherosclerosis

In November 2018, as a result of negotiations between representatives of the Polish Cardiac Society and the Polish Lipid Association with the Ministry of Health and the National Health Fund, a drug program called B.101 for treatment of patients with the most severe lipid disorders with modern therapy has been initiated. Initially, it was intended only for patients diagnosed with FH. Currently, it includes treatment with PCSK9 protein inhibitors and inclisiran in patients with FH and patients after myocardial infarction.

Previous studies show that the treatment available in the B.101 drug program achieves the therapeutic goal in up to 90% of patients with lipid disorders, especially in ACS arm [9].

Patients eligible for the program must be treated with a maximally tolerated dose of a potent statin (unless intolerance is present, in which case they receive a maximally tolerated dose) for at least three months, including combination therapy with ezetimibe for at least one month. According to the program criteria, it is not possible to treat any patient only with PCSK9 inhibitors or inclisiran without a concomitant statin unless the patient has a complete and documented intolerance to this group of drugs [47].

Data from the first four years of the program indicate that the survival probability of patients who participate in the B.101 program is 97%. Still, analysis of the detailed data for diagnoses I21 (myocardial infarction) and I63 (cerebral infarction) shows that these incidents occurred in only selected patients treated in the B.101 program.

According to data from the MACAMIS (KOS-Zawał) program, only 1.1% of patients participating in the program met the current B.101 inclusion threshold of 100 mg/dl (2.5 mmol/l). In comparison, 17% of patients met the threshold of 70 mg/dl (1.8 mmol/l) after 12 weeks. Such results, without doubt, overestimate these numbers if the assessment occurred after 6 or 12 months. Still, in the majority of cardiology departments, at 12 months after ACS, up to 30% of patients do not have the LDL-C levels lowered to less than 100 mg/dl (2.5 mmol/l), and 55% have LDL-C >70 mg/dl (1.8 mmol/l) [11].

In other Central and Eastern European countries, up to 70–90 patients per 100 000 population are treated with PCSK9 inhibitors, compared with 2–3 patients per 100 000 in Poland [48].

The most important reasons for such poor recruitment to the program are:

- insufficient patient education about treatment. It is necessary to intensify the activities of Scientific Societies to better educate patients about lipid disorders and methods of their treatment, including access to modern therapies;
- lack of information and knowledge about the program among cardiologists, also diabetologists, neurologists, vascular surgeons, general practitioners, and internists;
- too few centers enrolling patients in the program — 118 mainly cardiological centers are currently involved (data from April 2024);
- overly restrictive inclusion criteria and thresholds for LDL-C levels;
- inability to include patients with a history of myocardial infarction more than two years before inclusion;
- lack of availability of genetic testing in patients with FH;
- therapeutic inertia;

- a lot of false information and hypotheses that patients encounter in the media and at social gatherings.

Expansion of the B.101 program to include other therapeutic areas would also make it possible to significantly reduce deaths from other atherosclerotic diseases than just myocardial infarction, bearing in mind that in Poland, there were 160 000 deaths from cardiovascular incidents in 2023 [7, 8].

Proposals for a new interdisciplinary strategy for the modern therapy of lipid disorders in patients with multi-bed atherosclerosis

Patients with atherosclerotic cardiovascular disease are at very high risk, and the presence of comorbidities increases this risk 2–3 times [47]. For this reason, it should be possible to include a wider group of patients with very high cardiovascular risk for appropriate treatment of lipid disorders [49, 50].

The atherosclerotic cardiovascular disease most often involves several vascular beds, including the peripheral vasculature, and patients are managed by physicians of different specialties, not only within cardiology but also diabetology, nephrology, neurology, internal medicine, or vascular surgery clinics. For this reason, it is essential that the various specialists, including diabetologists, neurologists, nephrologists, and vascular surgeons, cooperate and are allowed to include their patient's modern treatment.

Current recommendations from national and international scientific societies make it clear that the primary and most critical goal of lipid disorder treatment is to reduce LDL-C levels, according to the principles of "the less, the better", "the sooner, the better" and "the longer, the better", which indicate the need to continue infinite treatment for life [51, 52]. Current treatment goals, based on large groups of patients, are very rigorous and can only be achieved by using potent drugs at high doses or a combination of both [4]. Currently, available evidence from meta-analyses indicates that the clinical benefit of statin treatment is mainly independent of the type of statin (the so-called class effect) but depends on the absolute reduction of LDL-C concentrations. In light of the currently available results of randomized trials, it seems that this formula should be extended to all non-statin drugs [53]. In the case of lipid disorders, it is necessary to recommend intensive hypolipemic treatment (not only intensive treatment with statins as has been the case for years) to achieve the lowest possible LDL cholesterol concentration. Such a strategy seems to be the only potentially successful in reducing the risk of cardiovascular incidents even in every second patient (by reducing the risk by 50%–55%). Additionally, such therapy is the most potent available at present [54].

It has been scientifically proven that low LDL-C levels are safe for patients. In the FOURIER trial, conducted on 25 982 patients [55], a progressive decrease in LDL-C levels was achieved in patients treated for four years with statins and PCSK9 inhibitors. A significant reduction followed in the risk of cardiovascular events. Reduction of LDL-C levels to values as low as <19 mg/dl (<0.5 mmol/l) translated into the most significant reduction in the risk of a major cardiovascular incident; moreover, achieving such low LDL-C concentrations was not associated with any adverse effects of therapy. With a median follow-up period of 2.2 years, no safety issues were identified in patients who achieved very low LDL-C levels. More recently, the safety of such intensive hypolipemic therapy was confirmed in the FOURIER-OLE trial with evolocumab with a maximum follow-up of 8.6 years [56], in the EBBINGHAUS-OLE trial with a follow-up of more than seven years [57] and in a pooled analysis of all available trials with inclisiran (3576 patients, follow-up time up to 6 years) [58]. The latter study also confirmed that the impact of anti-drug antibodies (ADA) should not be of concern, as they were present in only 1.4% of patients [58].

FINAL MESSAGE

Multi-bed atherosclerosis occurs in a significant percentage of patients with cardiovascular diseases. Some patients are not treated optimally despite the possibilities offered by the guidelines of Scientific Societies and the possibilities of reimbursement within the National Health Fund. Cooperation between doctors of many specialties (cardiologists, diabetologists, nephrologists, vascular surgeons, pediatricians, etc.) should be tightened in order to improve the effectiveness of treatment and better educate both the medical community and the patients being treated.

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