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Assessment of application of the new 2019 European Society of Cardiology/ European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias in daily clinical practice — one center study

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Abstract: Background: Cardiovascular diseases are the first cause of death globally. Hypercholesterolemia is the most important factor responsible for atherosclerotic plaque formation and increasing cardiovascular risk. Reduction of LDL-C level is the most relevant goal for reduction of cardiovascular risk.
Aims: Real life adherence to guidelines concerning statin therapy in one center study population.
Methods: We analyzed data collected in the Department of Internal Diseases from September 2019 to February 2020, obtained from 238 patients hospitalized in this time period. We assessed application of the new 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias in daily clinical practice and compared effectiveness of LLT according to 2016 and 2019 guidelines.
Results: Only 1 in 5 patients with dyslipideamia achieve the 2019 ESC/EAS guideline-recommended levels of LDL-C with relation to their TCVR. We noticed that 20 of patients who did not achieve proper 2019 LDL level, meet the therapy targets established in year 2016. We observed that higher patient TCVR resulted in better compliance with guidelines and ordination of proper LLT. Most patients were on monotherapy with statins.
Conclusions: It could be beneficial to start treatment with double or even triple therapy especially in group with the highest LDL-C levels.

Key words: cardiovascular risk, ESC/EAS guidelines, lipid-lowering therapy, PCSK9 inhibitors, statins.

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Introduction

Cardiovascular diseases are the first cause of death in the developed countries. They cause 17.9 mln deaths each year and 4 in 5 of these are caused by myocardial infarction or stroke [1]. Ischemic heart disease is also one of the most common causes of premature deaths in Poland [1, 2]. Hypercholesterolemia is the most important factor responsible for atherosclerotic plaque formation and increasing cardiovascular risk [3]. Reduction of LDL-C level is the most relevant aim for reduction of cardiovascular risk [4]. European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) provides guidelines for the management of dyslipidaemias with updates every 4–5 years and recommends therapy strategies and therapy targets according to the patient's cardiovascular risk levels. Despite that, studies on lipid disorders in Poland shows that the level of control of dyslipidemias is unsatisfying.

The NATPOL 2011 survey found that the percentage of patients receiving lipid-lowering therapy (LLT) — statins or fibrates — and treated unsuccessfully (with TC ≥190 mg/dL) was 8.1% [5].

Two other cross-sectional studies of the polish population's lipid disorders WOBASZ and WOBASZ II concluded that 60.6% of persons with hypercholesterolemia were not aware of the condition and only 6% were treated and achieved the treatment target. In years 2013–2014 compared to 2003–2005 there was an increase in the percentage of persons aware of having hypercholesterolemia and of those treated (also effectively treated) [6].

The aim of our study was to assess application of the new 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias in daily clinical practice [7]. We also compared effectiveness of LLT according to 2016 and 2019 guidelines to find out how many patients met new therapy targets [7, 8].

Materials and Methods

We conducted retrospective study analysis of data collected in the Department of Internal Diseases from September 2019 to February 2020. Data were obtained from 238 consecutive patients hospitalized in this time period. Collected data include sex, age, ischemic heart disease (IHD), myocardial infarction (MI), stroke/transient ischemic attack (TIA), percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG) history, invasive vascular interventions due to peripheral artery disease (PDA), early onset of atherosclerotic cardiovascular disease (ASCVD), first-degree relative with early onset of ACSVD, chronic kidney disease (CKD), diabetes mellitus (DM), complications of DM, presence of known hypertension (HT), lipid profile, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate

(HR),tobacco addition, treatment before admission to hospital and therapy ordered after hospitalization.

Firstly, we performed analysis according to 2019 ESC guidelines [7]. We assessed each patient's total cardiovascular risk (TCVR) and identified patients with dyslipidaemia. Then we evaluated appropriate LLT in relation to patient TCVR and LDL-C levels. Finally, we compared prescribed LLT with evaluated strategy and assessed the degree of achieving the goal of therapy. Secondly, we repeated each analysis according to 2016 guidelines [8].

Statistical analysis

Group of treated patients that achieved and that did not achieve lipid lowering therapy targets were compared. Analysis were conducted according to LDL-C target levels defined in 2019 and 2016 guidelines separately. Categorical data were summarized as percentage while continuous data as arithmetic mean with standard deviation. Differences in categorical variables were tested by χ^2 test with Pearson modification whereas in continuous variables with Mann-Whitney U test. A p-value ≤ 0.05 was considered significant. Statistical analyses were conducted using Statistica software ver. 13.1.

Results

There were 328 patients, 120 men and 118 women, mean age 66 years (range 22–97).

Characteristics of and illness burden is shown in Table 1. Only 6% of patients had ASCVD diagnosed in young age (ASCVD diagnosed in men <55 years and in women <60 years) and 13% had first-degree relatives with early onset of atherosclerotic vascular disease. Mean values of lipid profile and blood pressure are shown in Table 2.

Table 1. Characteristic of and illness burden among patient population.

Characteristic	Number and percentage (%) of patients
IHD	84 (35)
MI	44 (18)
stroke/TIA	25 (11)
CKD (stage 2–4)	55 (23)
DM	112 (47)
DM complications	29 (12)
HT	176 (74)
PCI	24 (10)
CABG	10 (4)

Table 1. cont.

Characteristic	Number and percentage (%) of patients
invasive vascular intervention due to PDA	2 (1)
Tobacco addiction	130 (55)

IHD — ischemic heart disease, MI — myocardial infarction, TIA — transient ischemic attack, CKD — chronic kidney disease, DM — diabetes mellitus, HT — hypertension, PCI — percutaneous coronary interventions, CABG — coronary artery bypass grafting, PDA — peripheral artery disease

Table 2. Lipid profile and blood pressure values among patient population.

Parameter	Mean value	SD
Total cholesterol (mg/dL)	167.93	58.18
HDL-C (mg/dL)	41.41	15.91
LDL-C (mg/dL)	101.97	45.96
TG (mg/dL)	130.76	85.28
SBP (mmHg)	129	24.24
DBP (mmHg)	78	13.14
HR (beats/min)	86	15.23

HDL-C — high-density lipoprotein cholesterol, LDL-C — low-density lipoprotein cholesterol TG — triglycerides, SBP — systolic blood pressure, DBP — diastolic blood pressure, HR — heart rate

According to 2019 guidelines 64% of patients had very high cardiovascular risk. 191 patients with dyslipidaemia were identified. As much as 71% of them had prescribed lipid lowering therapy (pharmacological treatment, lifestyle modification or both) and 29% did not receive any therapy even though it was necessary. In the group with prescribed lipid lowering therapy, 29% reached therapy targets and 71% did not (Fig. 1). Statistically significant differences between groups that achieved and that did not achieve therapy targets are shown in Table 3 and Fig. 2.

According to 2016 guidelines 72% of patients had very high cardiovascular risk. 191 patients with dyslipidaemia were identified. As much as 72% of them had prescribed lipid lowering therapy (pharmacological treatment, lifestyle modification or both) and 28% did not receive therapy despite such necessity. In the group with ordered lipid lowering therapy 45% reached therapy targets and 55% did not (Fig. 1). Statistically significant differences between groups that achieved and that did not achieve therapy targets is shown in Table 4.

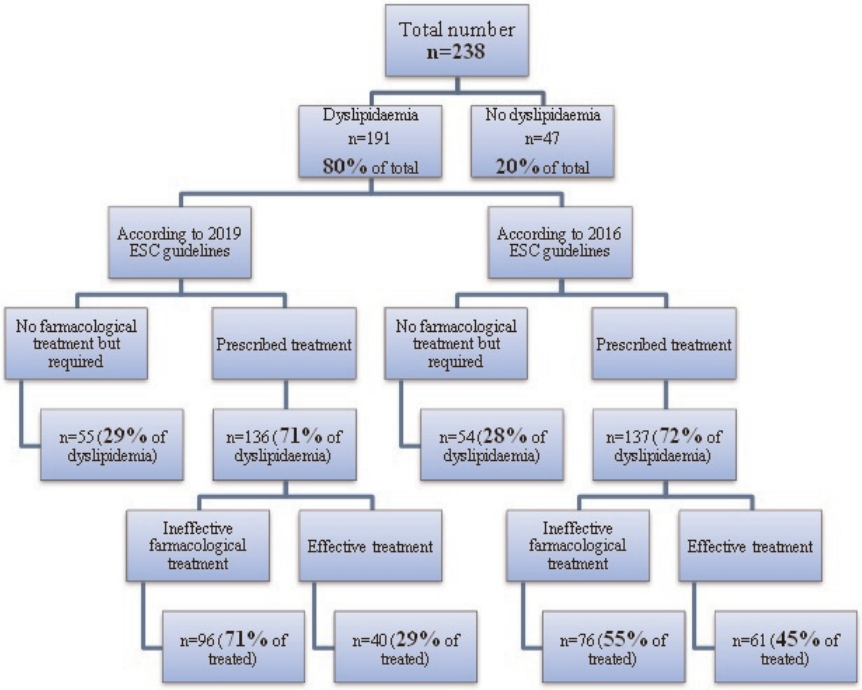

Fig. 1. Prevalence of dyslipidaemia and effectiveness of LLT among patient population according to 2019 and 2016 guidelines.

Table 3. Statistically significant differences between groups that achieved and that did not achieve therapy targets according to 2019 guidelines.

Characteristic	Achieved therapy targets	Did not achieve therapy targets	p-value
% of patients with IHD	18	55	p <0.001
% of patients with MI	10	31	p = 0.009
% of patients with very high TCVR	40	84	p <0.001
% of patients with HT	60	86	p <0.001
Mean age (years)	59	70	p <0.001
Mean total cholesterol level (mg/dL)	150.08	184.39	p <0.05
Mean LDL-C level (mg/dL)	83.20	112.95	p <0.001
Mean SBP (mmHg)	118	133	p <0.05

IHD — ischemic heart disease, MI — myocardial infarction, TCVR — total cardiovascular risk, HT — hypertension, LDL-C — low-density lipoprotein cholesterol, SBP — systolic blood pressure

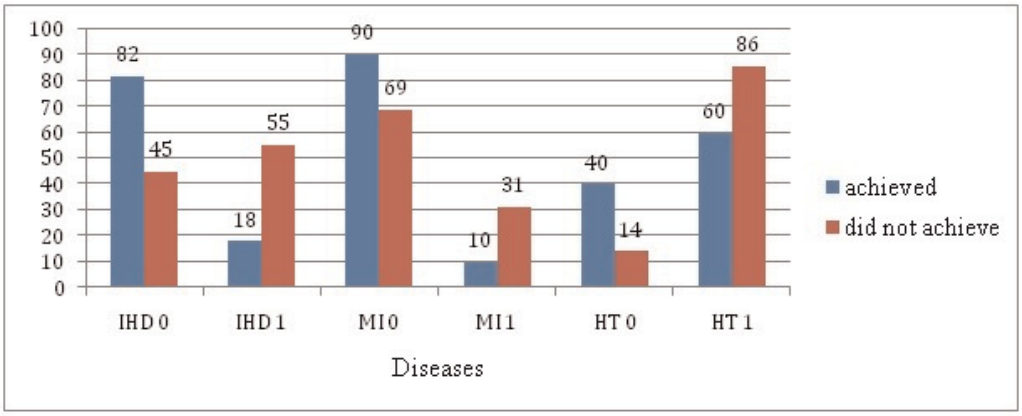

Fig. 2. Percentage (%) of patient with or without IHD, MI and HT in group that achieved vs. did not achieve 2019 therapy target.

Table 4. Statistically significant differences between groups that achieved and that did not achieve therapy targets according to 2016 guidelines.

Characteristic	Achieved therapy targets	Not achieved therapy targets	p-value
% of patients with very high TCVR	67	89	p = 0.009
% of patients with HT	70	86	p = 0.032
Mean total cholesterol level (mg/dL)	143.52	199.57	p <0.001
Mean LDL-C level (mg/dL)	79.93	125.21	p <0.001
Mean HDL-C level (mg/dL)	39.59	44.68	p <0.025

TCVR — total cardiovascular risk, HT — hypertension, LDL-C — low-density lipoprotein cholesterol, HDL-C — high-density lipoprotein cholesterol

Comparing effectiveness of lipid lowering therapy according to 2019 guidelines with effectiveness according to 2016 guidelines we observed that 20 persons who did not achieve proper 2019 LDL-C level, meet the therapy target established in year 2016.

In the group that achieved the therapy target according to 2019 guidelines 23% were taking statins before hospitalization (89% atorvastatin and 11% rosuvastatin). Dosage calculated to atorvastatin is shown in Fig. 3. None of our patients took ezetimibe or fibrates. In hospital 40% patients had been prescribed statins (94% atorvastatin and 6% rosuvastatin). Dosage calculated to atorvastatin are shown in Fig. 3. No one had ezetimibe or fibrates prescribed.

In the group that did not achieve the therapy target according to 2019 guidelines 27% were taking statins before hospitalization (65% atorvastatin, 19% rosuvastatin, 8% simvastatin and 8% unknown statin). Dosage calculated to atorvastatin is shown in Fig. 4.

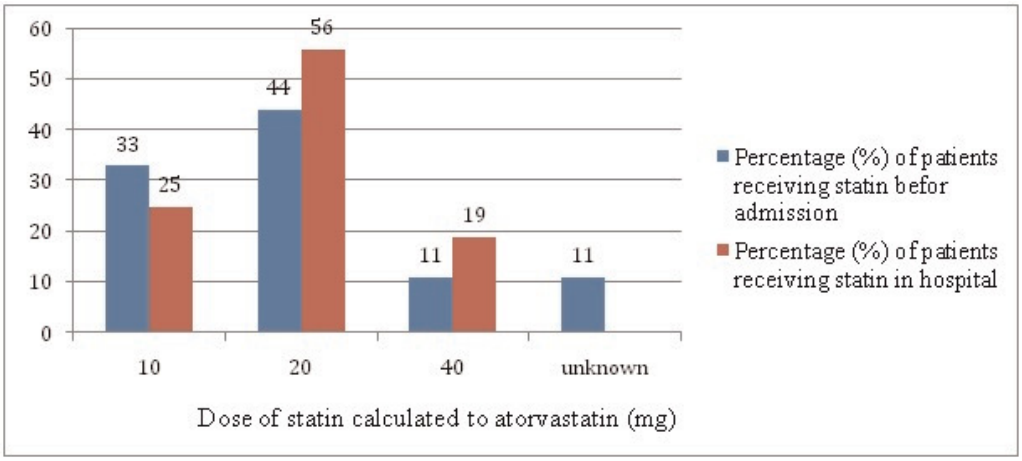

Fig. 3. Percentage (%) of patients receiving statin before admission to hospital and during hospitalization by doses of drug in group that achieved therapy targets according to 2019 guidelines.

Fibrates were prescribed in 5% patients and 2% take ezetimibe as triple therapy. During hospital stay 91% patients had been prescribed statins (77% atorvastatin and 23% rosuvastatin). Dose calculated to atorvastatin is shown in Fig. 4. Fibrates were prescribed in 2% of patients and 1% had ezetimibe as triple therapy.

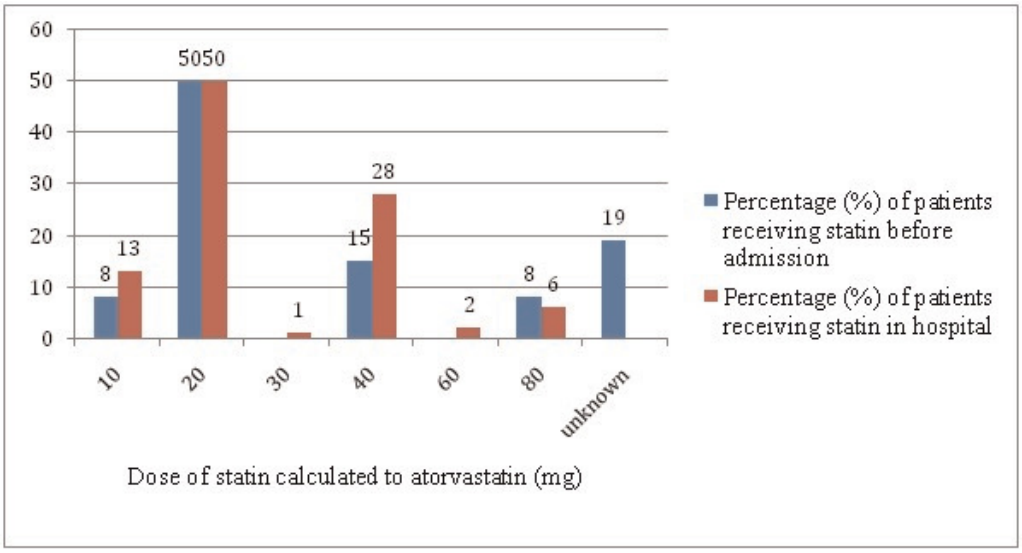

Fig. 4. Percentage (%) of patients receiving statin before admission to hospital and during hospitalization by doses of drug in group that did not achieve therapy targets according to 2019 guidelines.

Discussion

Scientific evidence shows that the lower the LDL-C level the better it is for effective cardiovascular risk level reduction and risk of cardiovascular mortality [4, 9–12]. At the same time studies have shown that even very low LDL-C values were found to have no adverse effect for patients [11, 13]. Because of that subsequent guidelines for management of dyslipidaemias recommend lower LDL-C values as therapeutic targets for individual groups of cardiovascular risk. Current guidelines set more restrictive lipid lowering therapy targets compared to that of 2016. At very high TCVR group it is recommended to achieve ≥50% reduction from baseline and LDL-C level <55 mg/dL, and in high TCVR group ≥50% reduction from baseline and LDL-C level <70 mg/dL [7, 8]. More restrictive desired LDL-C levels result in more challenging clinical targets to achieve. Our data analysis shows that only 1 in 5 patients with dyslipideamia achieve the 2019 ESC guideline-recommended levels of LDL-C with relation to their TCVR. Also, another studies shows that unsatisfying number of patient achieve recommended therapy targets in Poland and in other countries [5, 6, 14, 15]. Current guidelines recommend to start pharmacotherapy with the highest tolerated dose of statin and ad ezetimibe firstly and inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9) — PCSK9i, secondly when target is not reached [7]. For this reason, it may be beneficial to start the therapy with double (statins with ezetimibe) or even triple therapy (statins with ezetimibe and PCSK9i) in the first regiment. That strategy could help reduce the time needed to achieve therapy targets. Moreover, current guidelines divide patients into 4 groups regarding to their cardiovascular risk [7]. It could be justified to separate groups of patients with extremely high cardiovascular risk — patients with a history of serious cardiovascular events and with significantly elevated LDL-C level. This approach can help identifying patients for whom rapid reduction of LDL-C level is particularly important.

As mentioned above new drugs may be helpful in achieving desirable LDL-C levels more effectively. In recent years, PCSK9i give promising results [16, 17]. These are monoclonal antibodies that act on the PCSK9 protein. Reduction of the concentration of this protein in plasma increases LDL receptors (LDLR) expression what resulting in LDL-C levels reduction [7]. Alirocumab and evolocumab were approved by the FDA in 2015 year [18]. PCSK9 inhibitors allow to achieve very low levels of LDL-C and reduce residual cardiovascular risk that remain despite statin-based LLT. They are used mainly in patients who do not achieve the appropriate level of LDL-C and in people who are at extreme risk of cardiovascular risk, including familial hypercholesterolemia [7, 19]. Easy administration, subcutaneous injection every 2 weeks or once a month, can be advantage of these drugs because of better control of the administrated dose [20]. Studies have shown that, depending on the dose, PCSK9i reduce LDL-C levels by an average of 60%. PCSK9i combined with high or even maximally

tolerated doses of statins compared with placebo and compared with ezetimibe, reduced plasma LDL-C by 46–73% and 30%, respectively [7]. In EVOPACS study effectiveness of evolocumab in patients with acute coronary syndrome (ACS) was assessed. The drug was administered after admission to hospital and after 4 weeks. LDL-C levels was assessed after 8 weeks. Mean LDL-C levels decreased from 140 mg/dL to 31 mg/dL in the evolocumab group, and from 132 mg/dL to 80 mg/dL in the placebo group. The difference in mean percentage change from baseline in LDL-C levels was about 40.7% (95% CI: –45.2 to –36.2; p <0.001). Study shows that 95.7% of patients in the evolocumab group achieved LDL-C <70 mg/dL at week 8 compared to 37.6% in the placebo group [21]. FOURIER study showed that evolocumab is effective in reducing serious cardiovascular events risk. Comparing to placebo, evolocumab significantly reduced the risk of the primary end points (first serious cardiovascular events — cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) (9.8% vs. 11.3% of patients; HR 0.85; 95% CI, 0.79 to 0.92; p <0.001). This study also showed that achieving very low LDL-C levels is safe for patients [22]. Prespecified Analysis From the FOURIER Trial also showed that evolocumab reduces the total number of cardiovascular events — first and subsequent (total events, n = 2192 vs. n = 2714, RR 0.82, 95% CI 0.75–0.90, p <0.001) [23]. The ODYSSEY study showed effectiveness of alirocumab — second PCSK9i. It significantly reduces ischemic events and mortality in patients with an ACS occurred in preceding 1–12 months compared to placebo. The primary outcome, major adverse cardiac events (MACE), for alirocumab vs. placebo group of patients was 9.5% vs. 11.1% respectively (HR 0.85, 95% CI 0.78–0.93, p <0.001). LDL-C levels reduction in alirocumab vs. placebo group was at 4 months — 37.6 mg/dL vs. 93.3 mg/dL (62.7% reduction), at 48 months — 53.3 mg/dL vs. 101.4 mg/dL (54.7% reduction). The highest benefit achieved patients with baseline LDL-C ≥100 mg/dL. It is worth noting that this study also demonstrated a therapeutic benefit of lowering Lp (a) independent of LDL-C [24, 25].

Inclisiran is another drug which effectiveness has been studied in patients with the heterozygous form of FH. This drug is a small interfering RNA molecule (siRNA) that inhibits PCSK9 synthesis and thus reduces LDL-C level.ORION-9 study showed a significant reduction in LDL-C level in group receiving inclisiran compared to placebo in patients with FH. On day 510 after drug administration the percentage change in LDL-C was a reduction of 39.7% (95% CI, –43.7 to –35.7) in inclisiran group and an increase of 8.2% (95% CI, 4.3 to 12.2) in the placebo group [26].

Bempedoicacid is a novel drug that inhibits the action of ATP citrate lyase (cytosolic enzyme upstream of HMG-CoA reductase) what result in cholesterol synthesis inhibition [7, 27].When used as monotherapy, it reduces LDL-C levels by approximately 30% and in combination in ezetimibe by about 50% [7]. CLEAR Tranquility, a phase 3 study showed that bempedoic acid added to ezetimibe in patients with

hypercholesterolemia and statin intolerance result in LDL-C level reduction by 28.5% more comparing to placebo (–23.5% bempedoic acid, +5.0% placebo; p <0.001) [28]. Another phase 3 study assessed effectiveness of bempedoic acid in patients with hypercholesterolemia and ASCVD or with heterozygous familial hypercholesterolemia (HeFH) or both who receive statins and in patients with hypercholesterolemia with statin intolerance who receive maximally tolerated statin doses. In patients without statin intolerance baseline LDL-C level was 107.6 mg/dL. At week 12, the LDL-C level percentage change from baseline was −16.0% in the bempedoic acid vs. 1.8% in the placebo group (difference −17.8%; 95% CI, −19.5% to −16.0%; p <0.001). Patients with statin intolerance had a mean baseline LDL-C level of 144.4 mg/dL. The percentage changes in LDL-C levels at week 12 were −23.0% in the bempedoic acid and 1.5% in the placebo group (difference −24.5%; 95% CI, −27.8% to −21.1%; p <0.001). The decrease in LDL-C levels with bempedoic acid was sustained during long-term follow-up in both groups (in the group receiving a maximally tolerated statin doses — difference of −12.7% at week 52; in the group with statin intolerance — difference of −22.2% at week 24) [29].

Summarizing, scientific evidence show that novel lipid-lowering drugs can improve effectiveness of LLT, even in group of patients that are statin intolerant, but the economic barrier for now reduces their widespread use, especially for PCSK9i and inclisiran [7, 30].

Limitations

This study has potential limitations. Despite examining majority of patients hospitalized in the selected time period, sample of patients can be not representative for all population of patients receiving LLT. Further studies on bigger population may alter our observations. Data collected from anamnesis could be incomplete and percentage of patients e.g. that are smokers or had first-degree relative with premature ASCVD can be underestimated.

Conclusions

Majority of patients hospitalized at the Department of Internal Medicine had dyslipidaemia. Only 1 in 5 patients with dyslipideamia achieved the 2019 ESC/EAS guideline-recommended levels of LDL with relation to their TCVR. Previous history of serious cardiovascular events, cardiovascular disease and invasive interventions (PCI) in patients resulted in better compliance with ESC/EAS guidelines for the management of dyslipidaemias. It could be beneficial to recommend combined LLT as first-line treatment especially in patients with very high LDL-C levels and high cardiovascular risk. LLT can be extended with new classes of drugs that can improve treatment's effectiveness.

Authors contributions to the work

P.C. — collecting data, statistical analysis, data interpretation, manuscript preparation; A.C. — collecting data, statistical analysis; I.P. — collecting data, manuscript preparation; M.Z. — study design, collecting data; M.D.-Ś. — collecting data, manuscript preparation; Z.S. — study design, manuscript correction, supervisor

Conflict of interest

None declared.

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