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Article

Trends in the Management of Low-Density Lipoprotein Cholesterol in the Primary Healthcare Centre in Kaunas over the Five-Year Period

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Abstract: *Background and Objectives:* Low-density lipoprotein cholesterol (LDL-C) is a marker of cardiovascular risk and its management. This study evaluated LDL-C control trends in patients treated at a single healthcare centre in Lithuania. *Materials and Methods:* The study was conducted at the primary healthcare centre Saulės šeimos medicinos centras. Five-year (2019–2023) data on patients aged 40 years or older diagnosed with dyslipidaemia were extracted from a real-world data and analytics platform TriNetX. For analysis, patients were grouped into three groups: patients with dyslipidaemia only (control group), patients with dyslipidaemia and diabetes, and patients with dyslipidaemia and cardiovascular disease (CVD). The following LDL-C goals were used for analysis: < 1.4 mmol/L (a goal for very-high-risk patients in primary or secondary prevention), < 1.8 mmol/L (a goal for high-risk patients), and < 3.0 mmol/L (a goal for low-risk patients). *Results:* There were 18646 patients with dyslipidaemia. Of them, 8.9% of patients had diabetes and 3.1% of patients had CVD. The median LDL-C concentration was significantly lower in patients with diabetes (2.82 mmol/L, $p < 0.05$) and in patients with CVD (2.45 mmol/L, $p < 0.05$) than in the control group (3.35 mmol/L). A trend of decreasing median LDL-C over the years was observed in all groups, with the lowest median values in 2023. The proportion of patients with LDL-C level < 3 mmol/L increased from 32.0% in 2019 to 41.5% in 2023. The proportion of diabetic patients achieving LDL-C < 1.8 mmol/L increased from 7.4% to 25.9% and those achieving LDL-C < 1.4 mmol/L increased from 3.1% to 10.6%. The proportion of patients with CVD achieving LDL-C < 1.8 mmol/L increased from 14.2% to 36.6% and those achieving LDL-C < 1.4 mmol/L increased from 3.0% to 14.0%. *Conclusions:* Trends in the control of LDL-C levels are positive over 5 years, but a significant proportion of patients still did not reach the recommended target levels.

Keywords: diabetes; dyslipidaemia; low-density lipoprotein cholesterol; cardiovascular diseases; primary healthcare

1. Introduction

Despite the mortality due to cardiovascular diseases (CVD) has decreased in recent decades, CVD remain the main cause of mortality worldwide accounting for approximately a third of all deaths [1]. In 2021, there were 1.71 million deaths from CVD in the European Union (EU), equivalent to 32.4% of all deaths [2]. Lithuania ranked 4th in the EU with CVD mortality of 48.7% [2].

Dyslipidaemia, hypertension, smoking, overweight, and diabetes are the modifiable CVD risk factors accounting together for more than 50% of CVD cases and for 20% of deaths from any cause [3].

Low-density lipoprotein (LDL) together with other apolipoprotein B-containing lipoproteins are causal to the development of atherosclerotic CVD [4]. LDL cholesterol (LDL-C) serves as a marker of cardiovascular (CV) risk and its management [5]. Numerous clinical trials of lipid-lowering therapy (LLT) demonstrated a decreasing CVD incidence and mortality [6]. A meta-analysis of 38 randomized controlled trials of guideline-recommended LLTs (statins, ezetimibe, and proprotein convertase subtilisin-kexin type 9 inhibitors) reported that LDL-C reduction by 1 mmol/L resulted in a 22% lower risk for major vascular events (i.e., CV death, myocardial infarction, unstable angina, coronary revascularization, or stroke) [7]. Another meta-analysis (49 randomized controlled trials) reported similar risk reduction effects for statins and nonstatin interventions: the risk ratio for major vascular events per 1 mmol/L reduction in LDL-C level was 0.77 for statins and 0.75 for nonstatin interventions (i.e., diet, bile acid sequestrants, ileal bypass, and ezetimibe) [8].

Acknowledging the growing evidence of LDL-C's critical role in the development of CVD, the clinical guidelines have progressively introduced more stringent lipid management goals over the last decades [9]. Current European clinical guidelines recommend reducing LDL-C to the target levels based on individual CV risk [10,11]. The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidaemias [10] and the more recent ESC guideline on cardiovascular disease prevention [11] recommends LDL-C reduction of at least 50% from baseline and an LDL-C goal of < 1.4 mmol/L in very-high-risk patients, LDL-C reduction of at least 50% from baseline and an LDL-C goal of < 1.8 mmol/L in high-risk patients, and an LDL-C goal of < 3.0 mmol/L in low-risk patients. As per ESC/EAS guidelines, individuals with diabetes (type 1 or type 2), atherosclerotic CVD, chronic kidney disease or very-high levels of risk factors are considered being at very-high or high CV risk and require no further risk estimation [10].

Since primary healthcare plays an essential role in the identification of patients at risk, management of risk factors, and prevention of CVD [12–14], we evaluated LDL-C control over 5-year period in patients with dyslipidaemia treated at a primary healthcare center in Lithuania.

2. Materials and Methods

The study was conducted at the primary healthcare centre Saulės šeimos medicinos centras (Kaunas, Lithuania) which serves a total of 27,000 people.

Patients aged 40 years or older who were diagnosed with dyslipidaemia (code E78 according to the International Classification of Diseases, 10th revision [ICD-10]) were eligible for the study. Exclusion criteria were age below 40 years, oncological disease, severe autoimmune disease, palliative care patients, and pregnancy.

Within the study population, patients were grouped into three groups: i) a control group consisting of patients with dyslipidaemia only (no diabetes or CVD), ii) patients with dyslipidaemia and diabetes (ICD-10 codes E10 or E11), and iii) patients with dyslipidaemia and CVD (ICD-10 codes I25.2, I21, I70, I63, or Z95).

The LDL-C goals set by the 2019 ESC/EAS guidelines [10] and the 2021 ESC guidelines [11] were used for analysis: < 1.4 mmol/L, < 1.8 mmol/L, and < 3.0 mmol/L.

Data on patients' diagnosis, sex, age, and LDL-C concentration in the period from 2019 to 2023 were extracted from TriNetX, a real-world data and analytics platform. For patients having more than one LDL-C measurement within a calendar year, the latest value was used for analysis.

Data were analysed using the statistical software package SPSS version 29. Normality of distribution was assessed with the Kolmogorov-Smirnov test for samples larger than 50 and the Shapiro-Wilk test for samples between 30 and 50. Quantitative variables were presented as mean (standard deviation) in case of normal distribution or as median (first quartile and third quartile or interquartile range) in case of non-normal distribution. Qualitative data were presented as a number (n) and percentage (%). A nonparametric Kruskal-Wallis's test was used to compare quantitative variables among more than two groups. A Pearson's chi square test was used to compare qualitative variables.

Univariate and multivariate logistic regression analyses were done to identify independent variables that were associated with LDL-C values of < 3.0 mmol/L. The dependent variable was LDL-

C (< 3.0 mmol/L versus ≥ 3.0 mmol/L). The independent variables used in the univariate analysis were age, sex, diagnosis of diabetes, and CVD. Multivariate logistic regression was employed using the enter method, i.e., all variables that were significant in univariate analysis were entered into the model at the same time.

Statistically significant (two-sided $p < \alpha$) differences were interpreted at a 5% level of significance (i. e. $\alpha = 0.05$).

3. Results

The study population consisted of 18,646 patients with dyslipidaemia (one patient was excluded because of missing information on sex). There were 8.9% patients with type 1 or type 2 diabetes mellitus and 3.1% patients with CVD. Detailed information on the number of patients with specific ICD-10 codes is provided in Table 1.

The proportion of women was slightly higher (58.2%). The mean age was 58.1 years (range, 40 to 89 years).

Table 1. Sociodemographic and clinical characteristics of the study population.

Characteristics	
Women, n (%)	10,848 (58.2)
Men, n (%)	7,798 (41.8)
Age, mean (standard deviation), years	58.1 (12.3)
LDL-C concentration	
median (Q1, Q3), mmol/L	3.29 (2.6, 4.0)
< 3 mmol/L, n (%)	7,188 (38.5)
< 1.8 mmol/L, n (%)	1,219 (6.5)
< 1.4 mmol/L, n (%)	388 (2.1)
Patients with dyslipidaemia (no diabetes or CVD), n (%)	16,268 (87.2)
Patients with diabetes mellitus and CVD, n (%)	137 (0.7)
Patients with diabetes mellitus, n (%)	1,662 (8.9)
Type 1 diabetes mellitus (E10), n (%)	10 (0.05)
Type 1 diabetes mellitus with renal complications (E10.2), n (%)	7 (0.04)
Type 1 diabetes mellitus with ophthalmic complications (E10.3), n (%)	2 (0.01)
Type 1 diabetes mellitus with neurological complications (E10.4), n (%)	6 (0.03)
Type 1 diabetes mellitus with other specified complications (E10.6), n (%)	23 (0.12)
Type 1 diabetes mellitus without complications (E10.9), n (%)	10 (0.05)
Type 2 diabetes mellitus (E11), n (%)	4 (0.02)
Type 2 diabetes mellitus with coma (E11.0), n (%)	3 (0.02)
Type 2 diabetes mellitus with renal complications (E11.2), n (%)	19 (0.10)
Type 2 diabetes mellitus with ophthalmic complications (E11.3), n (%)	15 (0.08)
Type 2 diabetes mellitus with neurological complications (E11.4), n (%)	171 (0.92)
Type 2 diabetes mellitus with peripheral circulatory complications (E11.5), n (%)	3 (0.02)
Type 2 diabetes mellitus with other specified complications (E11.6), n (%)	206 (1.10)
Type 2 diabetes mellitus with unspecified complications (E11.8), n (%)	158 (0.85)
Type 2 diabetes mellitus without complications (E11.9), n (%)	1,162 (6.23)
Patients with CVD, n (%)	579 (3.1)
Acute transmural myocardial infarction of anterior wall (I21.0), n (%)	5 (0.03)

Acute transmural myocardial infarction of inferior wall (I21.1), n (%)	14 (0.08)
Acute transmural myocardial infarction of other sites (I21.2), n (%)	2 (0.01)
Acute transmural myocardial infarction of unspecified site (I21.3), n (%)	1 (0.01)
Acute subendocardial myocardial infarction (I21.4), n (%)	16 (0.09)
Acute myocardial infarction. unspecified (I21.9), n (%)	2 (0.01)
Old myocardial infarction (I25.2), n (%)	239 (1.28)
Cerebral infarction due to thrombosis of cerebral arteries (I63.3), n (%)	6 (0.03)
Cerebral infarction due to embolism of cerebral arteries (I63.4), n (%)	2 (0.01)
Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries (I63.5), n (%)	37 (0.20)
Other cerebral infarction (I63.8), n (%)	1 (0.01)
Cerebral infarction. unspecified (I63.9), n (%)	11 (0.06)
Sequelae of cerebral infarction (I69.3), n (%)	174 (0.93)
Atherosclerosis (I70), n (%)	11 (0.06)
Atherosclerosis of aorta (I70.0), n (%)	1 (0.01)
Atherosclerosis of renal artery (I70.1), n (%)	1 (0.01)
Atherosclerosis of arteries of extremities (I70.2), n (%)	51 (0.27)
Atherosclerosis of other arteries (I70.8), n (%)	3 (0.02)
Generalized and unspecified atherosclerosis (I70.9), n (%)	7 (0.04)
Presence of coronary angioplasty implant and graft (Z95.5), n (%)	132 (0.71)

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; Q, quartile.

In the whole study population, the median LDL-C concentration was 3.29 mmol/L and 38.5% of patients had LDL-C < 3 mmol/L (Table 1).

Within the whole 5-year period, the median (interquartile range) LDL-C concentration was significantly lower in patients with diabetes (2.82 [1.56] mmol/L, $p < 0.001$) and in patients with CVD (2.45 [1.53] mmol/L, $p < 0.001$) than in the control group (3.35 [1.34] mmol/L).

A general tendency of decreasing median LDL-C over the years was observed in all groups, with the lowest median values in each study group in 2023 (Table 2).

Table 2. Median LDL-C concentrations: comparison among years in each study group.

Study group	2019	2020	2021	2022	2023	p value ^a
Dyslipidaemia only, n (%)	n = 2,750	n = 2,509	n = 3,448	n = 3,748	n = 3,813	
	3.42 (1.31)	3.39 (1.31)	3.40 (1.32) ^b	3.41 (1.33)	3.21 (1.36) ^c	< 0.001
Dyslipidaemia + diabetes, n (%)	n = 257	n = 313	n = 348	n = 396	n = 348	
	3.20 (1.69)	2.93 (1.46) ^b	2.79 (1.48) ^b	2.87 (1.65) ^b	2.54 (1.42) ^c	< 0.001
Dyslipidaemia + CVD, n (%)	n = 134	n = 96	n = 116	n = 140	n = 93	
	2.62 (1.49)	2.60 (1.65)	2.35 (1.58)	2.39 (1.48)	2.17 (1.36) ^b	0.008

Values are medians (interquartile range). CVD, cardiovascular disease. ^ap value for difference among years in a given study group. p values for differences between specific years in a given study group: ^bp < 0.05 vs 2019. ^cp < 0.05 vs 2019, 2020, 2021, 2022.

When analysing data for the whole 2-year period, the proportion of patients achieving the target LDL-C levels was significantly higher among patients with diabetes or CVD comparing to the patients with dyslipidaemia only (control group) (Table 3).

Table 3. Number (%) of patients achieving different LDL-C targets in study groups in 2019-2023.

LDL-C target	Dyslipidaemia only n = 16,268	Dyslipidaemia + diabetes n = 1,662	Dyslipidaemia + CVD n = 579	p value ^a
< 3.0 mmol/L, n (%)	5,762 (35.4)	930 (56.0) ^a	401 (69.3) ^a	< 0.001
< 1.8 mmol/L, n (%)	755 (4.6)	274 (16.5) ^a	138 (23.8) ^a	< 0.001
< 1.4 mmol/L, n (%)	211 (1.3)	110 (6.6) ^a	50 (8.6) ^a	< 0.001

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. ^ap value for difference among study groups. ^bp < 0.05 vs control group (patients with dyslipidemia only).

The analysis of LDL-C targets achievement in each year showed that the proportion of patients achieving LDL-C of < 3.0 mmol/L in the patients with dyslipidaemia only (control group) was similar in 2019-2022, but it was significantly higher in 2023 than in the previous years (Table 4). Among patients with diabetes and CVD, the proportion of patients achieving LDL-C of < 1.8 mmol/L or < 1.4 mmol/L increased (with some fluctuations) over the years, but the most notable increase was also observed in 2023 (Table 3).

Table 4. Number (%) of patients achieving different LDL-C targets: comparison among years in each study group.

Study group	2019	2020	2021	2022	2023	p value ^a
LDL-C < 3.0 mmol/L						
Dyslipidaemia only, n (%)	n = 2,750 881 (32.0)	n = 2,509 848 (33.8)	n = 3,448 1209 (35.1)	n = 3,748 1243 (33.2)	n = 3,813 1581 (41.5) ^c	<0.001
Dyslipidaemia + diabetes, n (%)	n = 257 115 (44.7)	n = 313 166 (53.0)	n = 348 201 (57.8) ^b	n = 396 209 (52.8)	n = 348 239 (68.7) ^c	<0.001
Dyslipidaemia + CVD, n (%)	n = 134 91 (67.9)	n = 96 59 (61.5)	n = 116 79 (68.1)	n = 140 101 (72.1)	n = 93 71 (76.3)	0.225
LDL-C < 1.8 mmol/L						
Dyslipidaemia only, n (%)	n = 2,750 93 (3.4)	n = 2,509 110 (4.4)	n = 3,448 163 (3.9)	n = 3,748 147 (3.9)	n = 3,813 242 (6.3) ^c	<0.001
Dyslipidaemia + diabetes, n (%)	n = 257 19 (7.4)	n = 313 44 (14.1)	n = 348 50 (14.4)	n = 396 71 (17.9) ^b	n = 348 90 (25.9) ^d	<0.001
Dyslipidaemia + CVD, n (%)	n = 134 19 (14.2)	n = 96 18 (18.8)	n = 116 28 (24.1)	n = 140 39 (27.9)	n = 93 34 (36.6) ^b	0.001
LDL-C < 1.4 mmol/L						
Dyslipidaemia only, n (%)	n = 2,750 15 (0.5)	n = 2,509 30 (1.2)	n = 3,448 43 (1.2) ^b	n = 3,748 53 (1.4) ^b	n = 3,813 70 (1.8) ^b	< 0.001
Dyslipidaemia + diabetes, n (%)	n = 257 8 (3.1)	n = 313 19 (6.1)	n = 348 15 (4.3)	n = 396 31 (7.8)	n = 348 37 (10.6) ^c	< 0.001
Dyslipidaemia + CVD, n (%)	n = 134 4 (3.0)	n = 96 7 (7.3)	n = 116 10 (8.6)	n = 140 16 (11.4)	n = 93 13 (14.0) ^b	0.034

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. ^ap value for difference among years in a given study group. p values for differences between specific years in a given study group: ^bp < 0.05 vs 2019, ^cp < 0.05 vs 2019, 2020, 2021, 2022, ^dp < 0.05 vs 2019, 2020, 2021, ^ep < 0.05 vs 2019, 2021.

In the univariate analysis, age, male sex, diagnosis of diabetes or CVD were all associated with higher odds ratios to reach LDL-C values of < 3.0 mmol/L (Table 5). All these variables remained significant in the multivariate analysis (Table 5).

Table 5. Univariate and multivariate logistic regression analysis for predicted LDL-C values of < 3.0 mmol/L.

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Age	1.009	1.007-1.012	< 0.001	1.003	1.000-1.005	0.046
Sex (male)	1.120	1.055-1.189	< 0.001	1.102	1.035-1.174	0.002
Diabetes	2.296	2.080-2.533	< 0.001	2.165	1.956-2.398	< 0.001
Cardiovascular disease	3.786	3.221-4.450	< 0.001	3.423	2.898-4.043	< 0.001

CI, confidence interval.

4. Discussion

The control of LDL-C levels in the single primary healthcare center improved over the five-year period. In the whole group of patients with dyslipidaemia, the proportion of patients with LDL-C level < 3 mmol/L increased from 32.0% in 2019 to 41.5% in 2023. The proportion of patients achieving more stringent goals set for high- and very-high-risk groups also increased. The achievement of LDL-C < 1.8 mmol/L increased 2.6-fold in patients with dyslipidaemia and CVD and 3.5-fold in patients with dyslipidaemia and diabetes. Similarly, the achievement of LDL-C < 1.4 mmol/L increased 4.7-fold in patients with dyslipidaemia and CVD and 3.4-fold in patients with dyslipidaemia and diabetes.

Recent data on LDL-C goals achievement in Lithuania are scarce. In the Lithuanian arm of an EUROASPIRE V (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) survey, only 4.5% of primary prevention patients reached their risk-based 2019 ESC/EAS LDL-C goal (21% of study population used statins) [15]. Earlier data from the Lithuanian High Cardiovascular Risk primary prevention program revealed that in 2009-2015 13.5% of middle-aged individuals without overt CVD had severe dyslipidaemia defined as total cholesterol ≥ 7.5 mmol/L, or LDL-C ≥ 6 mmol/L, or triglycerides ≥ 4.5 mmol/L [16]. A study on risk factor trends and mortality from non-communicable diseases in Lithuania observed a significant reduction in mean levels of LDL-C and total cholesterol between 1986 and 2008 [17]. In all three Baltic countries, less than 20% of primary care patients receiving LLT had LDL-C at the target level defined according to the 2011 ESC/EAS guideline [18].

Despite the positive trends observed in our study, the overall control of LDL-C levels remains far from optimal, with a significant proportion of patients still not reaching the recommended target levels. Real-world data from other European countries also shows insufficient dyslipidaemia control, even in the patients receiving LLT [19]. An EU-wide DA VINCI study found that only 33% of patients receiving LLT achieved their risk-based 2019 ESC/EAS LDL-C goal and goal achievement was even lower among patients at higher risk [20]. As per EUROASPIRE V survey, 46.9% of treated dyslipidaemic patients attained LDL-C target of < 2.6 mmol/L [21]. In high/very-high CV risk patients in Germany (36.3% of them were treated with LLT), 7.2% of patients attained LDL-C of < 1.8 mmol/L and 22.8% of patients had LDL-C from 1.8 to < 2.6 mmol/L [22]. In Portugal, a population-based cohort study analysed electronic health records of patients followed in both primary and secondary care and reported that LDL-C targets as per the 2019 ESC/EAS guidelines were achieved in only 44%, 27%, 7%, and 3% of low, intermediate, high, and very-high CV risk patients, respectively. Of note, the study population included both LLT-treated and untreated patients [23]. A SANTORINI study of patients with high- and very-high CV risk across 14 Central and Western European countries also reported a low proportion of patients (20.1%) achieving risk-based LDL-C goals as per the 2019 ESC/EAS guidelines. More than half of these patients were receiving LLT monotherapy and about one-fourth of patients were on combination LLT [24]. Even more concerning results were reported in a recent Belgium study, in which only 18% of patients with established atherosclerotic CVD receiving LLT had LDL-C of < 1.4 mmol/L [25].

In this study, we did not analyse the trends in LLT use among patients with dyslipidaemia. A significant increase in statin prescriptions (from 8.28 defined daily doses for a thousand inhabitants per day) in 2010 to 96.06 in 2021 was reported in Lithuania [26]. A similar increase in the use of LLT could be expected in our study population over the 5-year period. Increasing awareness of

cardiovascular risk management among healthcare providers and patients could also play a role in favourable trends observed in our study.

Noteworthy is the finding that the most notable achievement of LDL-C goals was observed in 2023. In the beginning of 2023 few significant changes in the national cardiovascular disease prevention program were implemented in Lithuania. These changes included extending age limits for a target population, risk-based frequency of medical examination, and financing of the program [27]. In addition, the reimbursement criteria for ezetimibe, a selective inhibitor of the intestinal absorption of cholesterol, were changed, allowing for its prescription to a larger population of patients (i.e. those with LDL-C ≥ 1.4 mmol/L despite the use of maximal tolerable doses of statins for at least 4 weeks). However, it is too early to speculate if these changes might have had such an immediate effect on LDL-C control levels and further observations of dyslipidaemia management trends are necessary to assess the impact of these governmental decisions.

Real-world evidence implies that LDL-C goals recommended by the current clinical guidelines are difficult to attain with LLT monotherapy [23], therefore less stringent reimbursement conditions facilitating the access to LLT other than statins and thus the possibility to prescribe combination therapy are necessary to improve LDL-C control.

Our study has several limitations. We analysed single-centre data; therefore, our findings cannot be generalized to the other healthcare centres or to the whole country. In addition, we defined study groups based on rather rough estimates of CV risk (i.e., presence or absence of diabetes or CVD diagnosis). Thus, our control group might have at least some patients at high- or very-high-risk (e.g., patients with chronic kidney disease or other significant CVD risk factors).

Despite these limitations, this analysis of medical records of the whole population of patients with dyslipidaemia treated at the single primary healthcare centre provides valuable insights on LDL-C management in a real-world setting. This helps to identify the gaps between the recommended LDL-C target levels and the actual rates of achieving these targets in routine care, as well as trends over time.

5. Conclusions

Analysis of LDL-C control in patients treated at the single healthcare centre in Lithuania demonstrated positive trends in the control of dyslipidaemia. However, a significant proportion of patients still did not reach the target levels recommended by current clinical guidelines, which highlights the necessity for enhanced efforts to further improve LDL-C management.

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Informed Consent Statement: Patient consent was waived because depersonalized patient data were used for analysis.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy and legal reasons.

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