Success in achieving LDL-C target values in a high-risk population in Slovakia: SlovakLipid retrospective study

Keywords
guidelines, cardiovascular risk, LDL, dyslipidaemia, target values

Abstract

Introduction
Slovakia belongs among the countries with the highest cardiovascular mortality, nevertheless extensive data on the effectiveness of dyslipidaemia management is lacking. The aim of this study was to assess the implementation of European guidelines in the very high-risk population in Slovakia.

Material and methods
We retrospectively analysed anonymised LDL C values of patients at very high cardiovascular risk gathered between 2017 and 2019 from collaborating laboratory with nationwide reach. CV risk was based on patient's ICD diagnoses. LDL C target values were based on the 2016ESC/EAS recommendations, as well as current recommendations from 2019. Patients diagnosed with ACS, stroke, or overall very high-risk CVD were selected.

Results
A total of 220 657 LDL-C test results from 72 039 patients were processed. Only 8 9% of patients with ACS attained target LDL-C in a follow-up test each year. 6-9% of patients had LDL-C levels ≥ 4.9 mmol/l. Only 9-10% of patients with stroke achieved target LDL-C levels, and 7-8% had levels ≥ 4.9 mmol/l. In the very high CV risk group, only 7% of patients achieved target levels, and 7-8% had extremely high LDL-C levels ≥ 4.9 mmol/l. With the ESC/EAS2019 recommendations only 2-3% of patients in each group achieved target levels each year.

Conclusions
Based on our results, we found that over 90% of patients with very high CVD risk do not achieve target LDL-C levels. This percentage is even higher when implementing the 2019 guidelines. These patients remain at high risk of subsequent CVD events and would benefit significantly from intensified hypolipemic therapy.

20th of July, 2023, Košice, Slovakia

Dear Editor

Dear reviewers,

thank you for your letter from 2nd of July 2023 on our manuscript No. AMS-15733-2023-01, "Success in achieving LDL-C target values in a high-risk population in Slovakia"

We were pleased to see that the interest rating was encouraging and following your letter we revised our paper to address the helpful and constructive comments.

We herewith submit the revised version hoping that the concerns have been adequately addressed and look forward to receiving your response.

With kind regards,

Štefan Tóth, asoc.Prof., MD, PhD, MPH

Response to editor:

Please consider citing the following papers:

https://pubmed.ncbi.nlm.nih.gov/35832716/; https://pubmed.ncbi.nlm.nih.gov/35316922/

https://pubmed.ncbi.nlm.nih.gov/34900032/; https://pubmed.ncbi.nlm.nih.gov/34482090/ ;https://pubmed.ncbi.nlm.nih.gov/30527895/

This article is of interest as it underlines that few very high-risk patients reach the LDL targets. Nevertheless, the discussion should be modified highlighting more the intervals between first event and LLT combinations, the use and timing of PCSK9i, and data from 2019 should be interpreted with cautious as guidelines were released in september 2019 therefore not applied in 2019.

Dear editor, we have added the suggested citations and

we have added in the discussion the following sentence:

…. However, this analysis is limited in part by the fact that older recommendations were still in effect in 2017, 2018, and up to September of 2019 so the data predicting the success in achieving of the target LDL-C according to the current guidelines need to be considered cautiously…..

Response to reviewer 1:

Methodology:

-The authors state that this is a retrospective analysis of large, anonymized data of LDL-C values, but on the same that the data were processed in anonymized form with the consent of all participants. At which time of presenting to the healthy system did the patients give informed consent for data use?

- Data were obtained in anonymous way in accordance with local regulations and international standards (one of the co-author is a lawyer – GDPR/medical law/patent law expert). Patients informed consent is not needed in this case of anonymous data and its processing.

Wording "with consent from all participants" means partners involved in our research - Novartis Slovakia Ltd and InovaHealth. We will reformulate this sentence in the text accordingly. – more closely explained in the following answer.

Changes in the text:
….. The data were processed in anonymised form with the consent of both Novartis Slovakia Ltd and InovaHealth….

… added co-author Dominika Zabavska….. Department of Business and Economic Law Faculty of Law, Pavel Jozef Šafárik University in Košice

-How was the ICD-10 code and the LDL-C-levels matched? Please explain this structure of the Slovakian health system.

Every blood sample of the patient needs to be sent with a certain diagnosis for processing – e.g. E78 hyperlipidemia, or just I10 hypertension (for prevention actions). Patients with stroke or acute coronary syndrome have the diagnoses mentioned in the lab test request. It can happen that later during the regularly check-ups, GPs or other specialists can give other diagnoses, but in the database was the patient already once mentioned under the diagnosis putting him into the high-risk category and the data could be matched and further analysed for the follow up.

-Please explain the rational to include Group 3.

We included group 3 because it has both stroke patients, and acute coronary syndrome patients but also patients with chronic coronary syndromes (after revascularisation of patients with severe coronary artery stenoses). Logically this could include the patients also with CCS without severe stenoses or just with one artery affected, but the general convention is to include only very high-risk patients, so the bias is only minimal.

Also, this group include the patients who did not have the laboratory test of LDL-C every year, so this group has higher number of patients/results included.

….. Group 3: consisted of patients who had any of the following diagnoses: I20.0, I21, I22, I25, I63.5, I63.8, and I63.9 on any laboratory test during 2017-2019 (this was the set of patients with a history of ACS, stroke and CCS) and had at least one LDL test during 2017-2019 at the same time…..

Results:

- For group 1+2, the inclusion criteria say: "and had at least one LDL-C test done in 2016" – however, these levels are not shown in the figures. Please present the levels in figure 1 and following.

Thank you for your suggestion.

The values from 2016 are not listed, as they were not influential (changes in comparison with the year 2016 were not statistically analyses – it was just an inclusion criteria), as the previous recommendations were only published in that year, so they should have had a real impact only in 2017-2018-2019... so it was important to monitor the changes in these years and monitor achievement in this period. In 2016, there would still be too much bias if the data were taken, as some patients could have already been applied, but not the majority. Similarly, it is also from 2019, where the new recommendations were published only at the end of the year, so the data for the new recommendations are only analysed with caution, which is also stated in the discussion.

- Please give n values for each group (text, table 1) and also for the number of LDL-C-values during follow up shown for example in figures 1/2/3.

Thank you, we have added:

In the table 1 there is: Number of patients (N)

…diagnosed ACS included N=1366 patients with…

…The group with diagnosed stroke included N=527 patients…

…A total of N=72 039 patients with 220 657 LDL-C measurements were include…

The values of LDL are in the chart - inside the bar

-Figure 5. What does CMP mean?

I apologize, it is a Slovak abbreviation for stroke. It is now corrected in the text. Thank You for the suggestion.

…. Fig. 5 Attainment of target LDL-C (mmol/L) values in 2017-2019 in group 2, in patients with dg. stroke with at least one examination in each year (n=231)….

Discussion:

-The discussion is appropriate regarding the subject but could be altogether shortened.

Thank you for the suggestions, we have shortened the discussion by almost 20% - almost 400 words, keeping the same level of information and including the suggested citations by the editor.

References:

Reference #7 cannot be obtained by common means, so please replace it.

Thank you, we have deleted the redundant reference and updated the rest.

To rule out bias during analysis, the authors should at least address the following items:

- ***"The authors used data made available and purchased by Novartis Slovakia Ltd. to prepare the article. " – Please explain how/on which legal base the data was collected by Novartis and according to which rule/ method the data distribution to the authors was performed.***

The data were obtained in anonymised form from Medirex by Innovahealth as part of statistical analyses, then the raw data were extrapolated into an Excel spreadsheet where each patient was assigned a random number and connected with their diagnosis, age, and LDL-C value. These data in the form of an anonymised Excel spreadsheet were purchased by Novartis on the basis

of a mutual agreement with the main author of this article for the purpose of determining the epidemiological situation in Slovakia. The data were subsequently processed by the lead author and prepared for publication by all co-authors.

Innovahealth provided consent for data processing and Novartis provided consent for free publication of the data.
Stated in the text:

In the material:… . The data were processed in anonymised form with the consent of both InovaHealth and MEDIREX group….

In the acknowledgement: ….The data were processed with the written consent of both Novartis Slovakia Ltd and InovaHealth….

The raw data were provided to the authors of the paper without any financial compensation and with the consent of all parties. - Please give an explanation about the company InovaHealth and by which administrative process the company obtained the lab data. Please give a short description about the work of the MEDIREX group.

The data were obtained in anonymised form from Medirex by Innovahealth as part of statistical analyses, then the raw data were extrapolated into an Excel spreadsheet where each patient was assigned a random number and connected with their diagnosis, age, and LDL-C value. These data in the form of an anonymised Excel spreadsheet were purchased by Novartis on the basis of a mutual agreement with the main author of this article for the purpose of determining the epidemiological situation in Slovakia. The data were subsequently processed by the lead author and prepared for publication by all co-authors. Innovahealth provided consent for data processing and Novartis provided consent for free publication of the data.

Medirex group is the leading company providing laboratory tests and diagnostic methods across the whole country (has the most results available). InovaHealth company did the processing of anonymized data provided by Medirex group. This anonymised data was then supplied to us (by Novartis) and further analysis was made by the authors of the study.

- ***Please give a short description of the funding agencies of the grants VEGA No 1/0700/23 and ACARDIO COVID 19.***

Both grants are funded by the Ministry of education of Slovakia – one grant – VEGA - is a "small grant" for pilot studies and the project ACARDIO COVID 19 is a structural fund, which was aimed to monitor the cardiovascular health before, during and after covid-19. (Lipid parameters years 2017-2018-2019) and during/after covid-19.

Reviewer 2:

Lowering LDL-cholesterol to a target value is of great importance to reduce cardiovascular risk. The assessment of this in some countries draws attention to how much work we still have in this regard

Lowering LDL-cholesterol to a target value is of great importance to reduce cardiovascular risk. The assessment of this in some countries draws attention to how much work we still have in this regard

Response to reviewer 2:
Thank you for your positive review.

Reviewer 3:

I've read with attention the paper entitled "Success in achieving LDL-C target values in a high-risk population in Slovakia: SlovakLipid retrospective study" that is potentially of interest. The background and aim of the study have been clearly defined. The methodology applied is overall correct, the results are reliable and adequately discussed. Given the mainly confirmative nature of the study, I suggest the authors to shorten the paper (in particular the discussion section) focusing on the main results. Then, it could be nice to add some recent papers published on the argument on the Arch Med Sci.

I've read with attention the paper entitled "Success in achieving LDL-C target values in a high-risk population in Slovakia: SlovakLipid retrospective study" that is potentially of interest. The background and aim of the study have been clearly defined. The methodology applied is overall correct, the results are reliable and adequately discussed. Given the mainly confirmative nature of the study, I suggest the authors to shorten the paper (in particular the discussion section) focusing on the main results. Then, it could be nice to add some recent papers published on the argument on the Arch Med Sci.

Response to reviewer 3:

Thank you for your suggestions. We have shortened mainly the discussion (by almost 20%, almost 400 words) and excluded several redundant sections, as well as we have added the citations of the several recent articles published in Arch Med Sci.

Reviewer 4:

a nice registry. only minor comment, in teh color key figure "AKS" is in place of ACS. then, the description of the second group varies in the figures and test. I think just prior stroke is simplest. but other places have dg. CMP , which I don't know what that is... so make sure it is all consistent. you have a nice discussion of this registry vs. other in Europe - that might make nice figure..

Response to reviewer 4:

Thank you for your review, we have corrected the abbreviations and added the figure comparing our results with other data in Europe.
Page 2 … **after the diagnosis ACS….**

Thank you for the suggestion, we have added the following table with the selected observational studies mentioned in the publication.

Tab. 3 Attainment of target LDL-C in the mentioned observational studies

(More details, selection criteria in the text and in the mentioned publications [16, 18, 19, 20, 21, 22, 23, 32])

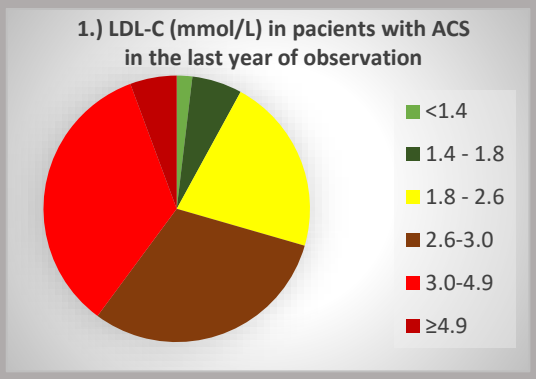
Study	Country	Number of observed patients	Attainment of target LDL-C valid in the years of the study
SlovakLipid	Slovakia	72 039	5%
EUROASPIRE IV [16]	24 European countries	16 426	19.5%
DYSIS II [18]	Belgium, France, Germany, Greece, Ireland, Italy Russia	880 ACS and 2778 CHD	ACS 23.2% CCS 29.6%
EUROASPIRE V [19]	27 countries in Europe	7824	30%
EPHESUS study [20]	Turkey	1868	18%
[21]	Germany	25 848 (ASCVD group)	8.5%
SAFEHEART [22]	Spain	4132 (HeFH)	11.2%
Da VINCI study [23]	14 European countries	9602	54% in primary prevention and 30% ASCVD (2016 guidelines) 33% in primary prevention, 18% with ASCVD (2019 guidelines)
Da VINCI study CEE [32]	Central and Eastern Europe (Czech Republic, Hungary, Poland, Romania, Slovakia, Ukraine	2154	60% in primary prevention and 31% in secondary prevention (2016 guidelines) 37% in primary prevention and 13% in secondary prevention (2019 guidelines)

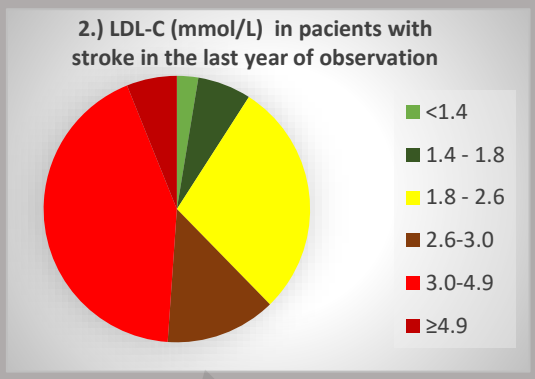
Success in achieving LDL-C target values in a high-risk population in Slovakia: SlovakLipid retrospective study

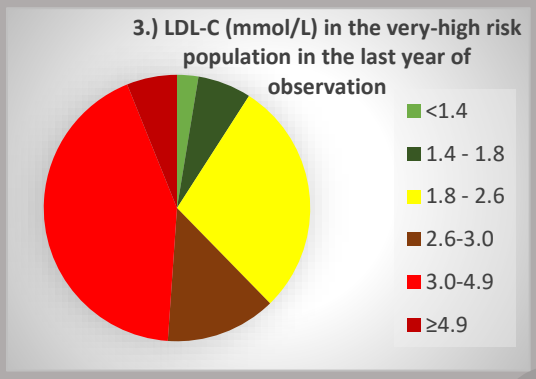
GRAPHICAL ABSTRACT

72 039 included very high-risk patients
220 657 LDL-C test results
3-year observation period

1.) Patients after the diagnosis ACS
2.) Patients after the diagnosis stroke
3.) Patients generally in the very high risk







- approximately 2% of patients in Slovakia reach the target LDL-C based on ESC/EAS 2019 guidelines; based on older guidelines it is 8%
- More than 6% of patients have LDL-C above ≥4.9 mmol/L
- Data could be applied also of other central and east European countries based on previous studies

Abstract

Introduction

Slovakia belongs among the countries with the highest cardiovascular mortality, nevertheless extensive data on the effectiveness of dyslipidaemia management is lacking. The aim of this study was to assess the implementation of European guidelines in the very high-risk population in Slovakia.

Material

We retrospectively analysed anonymised LDL-C values of patients at very high cardiovascular risk gathered between 2017 and 2019 from collaborating laboratory with nationwide reach. CV risk was based on patient's ICD diagnoses. LDL-C target values were based on the 2016ESC/EAS recommendations, as well as current recommendations from 2019. Patients diagnosed with ACS, stroke, or overall very high-risk CVD were selected.

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A total of 220 657 LDL-C test results from 72 039 patients were processed. Only 8-9% of patients with ACS attained target LDL-C in a follow-up test each year. 6-9% of patients had LDL-C levels ≥ 4.9 mmol/l. Only 9-10% of patients with stroke achieved target LDL-C levels, and 7-8% had levels ≥ 4.9 mmol/l. In the very high CV risk group, only 7% of patients achieved target levels, and 7-8% had extremely high LDL-C levels ≥ 4.9 mmol/l. With the ESC/EAS2019 recommendations only 2-3% of patients in each group achieved target levels each year.

Conclusion

Based on our results, we found that over 90% of patients with very high CVD risk do not achieve target LDL-C levels. This percentage is even higher when implementing the 2019 guidelines. These patients remain at high risk of subsequent CVD events and would benefit significantly from intensified hypolipemic therapy.

Keywords: guidelines, dyslipidaemia, cardiovascular risk, target values, LDL

INTRODUCTION

Based on prevalence studies, Slovakia belongs among countries with a high risk of CV disease, mortality, and morbidity. The annual incidence of CV mortality is 209.5 females and 333.8 males per 100 000 inhabitants [1]. Despite advances in both primary and secondary prevention, the decline in CV mortality is minimal. This is in marked contrast to the significant improvement in inpatient care of patients with acute CV events. This contradiction can be explained by inadequate control of risk factors in post-hospital, outpatient, and home settings [2]. One key factor is lipid profile control. However, the question remains as to where we stand in achieving target levels in the real population.

Dyslipidaemia is one of the major risk factors leading to the development of atherosclerotic cardiovascular disease (ACVD). When not treated properly, dyslipidaemia leads to ischaemic complications depending on the location [3, 4]. The relationship between LDL-cholesterol levels and the risk of major cardiovascular events is now clearly demonstrated by medical evidence. The reduction in the relative risk of ACVD is proportional to the absolute reduction of LDL-C and is not dependent on any particular treatment modality [5]. A significant decrease in LDL cholesterol leads to the stabilisation of atherosclerotic lesions. Using intravascular ultrasound, some forward studies have described that plaque regression can be observed thanks to either intensified statin [6], or anti-PCSK9 therapy [7]. Taking these findings into account, recent EAS/ESC recommendations have tightened LDL target levels. For high-risk patients, a 50% reduction in LDL from baseline is recommended in addition to target levels of 1.4 mmol/L LDL-C.

This study was aimed to retrospectively analyse an extensive amount of anonymised LDL-C values in individual populations of very high cardiovascular risk patients (as defined by guidelines). Another aim was also to determine the proportion of patients achieving LDL-C target values based on the recommendations in place at the time of each year of follow-up.

Patients and methods

Study design

This study was conducted as a retrospective analysis of large, anonymized data of LDL-C values of patients examined in outpatient and inpatient care throughout Slovakia. The data were obtained by *InovaHealth* from records of laboratory tests provided by MEDIREX Group. The data used in this study covered a three-year time interval between 2017 and 2019. This is the period in which the ESC/EAS 2016 guideline recommendations were in effect, and the second half of 2019 was based on the 2019 guidelines. The data were without regional or centre specificity. The data were processed in anonymised form with the consent of both Novartis Slovakia Ltd and InovaHealth. After the initial selection of suitable patients based on diagnoses that clearly showed very high CV risk, all LDL-C measurements of such identified patients from 2017 to 2019 were gathered, regardless of the diagnosis code at the time of LDL-C measurement. Patients were stratified by LDL-C values into the following intervals for better monitoring of LDL-C levels: < 1.4 mmol/l (<55mg/dL); 1.4 (inclusive) - 1.8 mmol/l (55 -70 mg/dL); 1.8 (inclusive) - 2.6 mmol/l (70 – 100 mg/dL); 2.6 (inclusive) – 3.0 mmol/L (100 – 115mg/dL), 3.0 (inclusive) – 3.5 mmol/L (115 – 135.34 mg/dL), 3.5(inclusive) – 4.0 mmol/L (135 – 155 mg/dL), 4.0(inclusive) – 4.9 mmol/L (155 – 190 mg/dL), above 4.9 mmol/L (above 190 mg/dL)

Eligibility criteria

Patients enrolled in this study were men and women of all ages but not younger than 18 years, meeting the characteristic of very high CV risk based on ESC/EAS [5]. Patients were included based on reported International Classification of Diseases (ICD) diagnoses.

The following groups of patients with very high CV risk were analysed:

- Group 1: patients who in 2017 had a laboratory test with any of the following diagnoses: I20.0, I21, or I22 (*history of ACS*) and had at least one LDL-C test done in 2016
- Group 2: patients who in 2017 had a laboratory test with any of the following diagnoses: I63.5, I63.8, and I63.9 (*history of stroke*) and at least one LDL-C test in 2016
- Group 3: consisted of patients who had any of the following diagnoses: I20.0, I21, I22, I25, I63.5, I63.8, and I63.9 on any laboratory test during 2017-2019

(*this was the set of patients with a history of ACS, stroke and CCS*) and had at least one LDL test during 2017-2019 at the same time.

Statistical processing

Descriptive statistics and methods designed to test statistical hypotheses were used to process the results. For categorical variables, the number and percentage of patients in each group are reported. To follow the dynamics of LDL-C in 2017-2019, patients with at least one LDL-C measurement in each year were included in the statistical analysis. Differences in the LDL-C values between the years in certain groups of patients were analysed by repeated measures of ANOVA Tukey post-hoc tests. In the analyses of LDL-C by age, the age of the patient as of the 1st of January 2019, was taken. Values of $p < 0.05$ were considered statistically significant. Attainment of target LDL-C values was calculated as a % value, including only the patients with an available LDL measurement in each year of the study.

Results

Patients' characteristics

In total, 72 039 eligible patients were enrolled from all the participating outpatient clinics and hospitals together with 220 657 LDL-C medical records. On average, each patient had 3.06 LDL-C tests done during the study period. Based on the protocol, we divided patients into groups based on CV disease type and then selected subgroups of patients with LDL-C measurement in each year of follow-up.

Tab. 1 Characteristics of each study group

	Group 1 – patients with dg. ACS	Group 2 – patients with dg. CMP	Group 3 – Patients generally at high risk of CVD
Number of patients (N)	1366	527	72 039
Number of records	5897	1905	220 657
Ration of men and women (%)	51% / 49%	50% / 50%	47% / 53%
Average number of LDL measurements	4.3	3.6	3.1
Representation of measurements in each year/only one/two (%)	50% / 27% / 23%	44% / 29% / 27%	33% / 41% / 26%
Mean LDL values in 2017/2018/2019 (mmol/L)	2.94/2.84/2.84	3.01/2.79/2.88	3.12/3.04/3.04
SD in 2017/2018/2019	1.11/1.07/1.06	1.09/1.05/1.13	1.07/1.04/1.05

The group of patients with diagnosed ACS included N=1366 patients with a total of 5897 LDL-C values, with an average of 4.3 measurements per patient over the entire study period and with an average LDL-C in each year 2017-2019 2.94/2.84/2.84 mmol/L (Fig. 1, Table 1). LDL-C levels decreased significantly (p=0.007) in 2018 in comparison with the year 2017, and in 2019 in comparison with 2017 (p=0.012). Between the years 2018 and 2019, no significant change was observed (p=0.99) (Fig. 1, Table 1). The group with diagnosed stroke included N=527 patients and a total of 1905 LDL-C values, with an average of 3.6 measurements per patient over the entire study period and with an average LDL-C in each year 2017-2019 3.01/2.79/2.88. LDL-C levels decreased significantly (p=0.0005) in 2018 in comparison with the year 2017. Between the years 2018 vs. 2019, 2017 vs. 2019 no significant change was observed (p=0.357; 0.088)) (Fig. 2, Table 1). The overall group of patients meeting the criteria for very high CV risk included patients with a history of ACS and/or stroke, as well as patients with a chronic coronary syndrome diagnosis based on ESC definitions. A total of N=72 039 patients with 220 657 LDL-C measurements were included in this group, with an average of

3.1 results per patient over the entire study period. The mean LDL-C values in this group over the study period were 3.30/3.21/3.18. LDL-C levels decreased significantly ($p < 0.0001$) in 2018 in comparison with the year 2017, and in 2019 in comparison with 2017 ($p < 0.0001$). Between the years 2018 and 2019, no significant change was observed (p=0.99) (Fig. 3; Table 1).

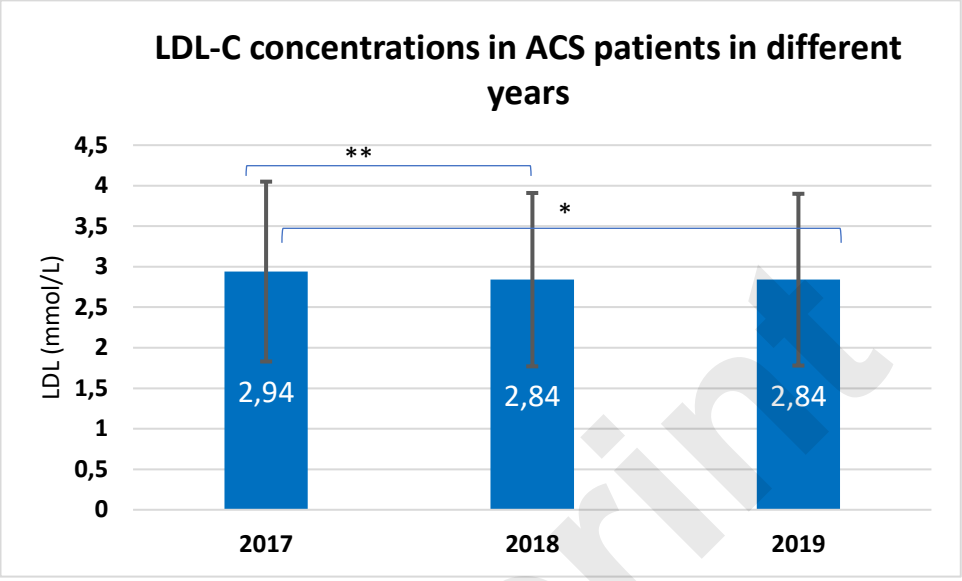

Fig. 1 Mean LDL-C (mmol/L) concentrations in ACS patients in different years after the initial diagnosis from all the obtained data from all specialists

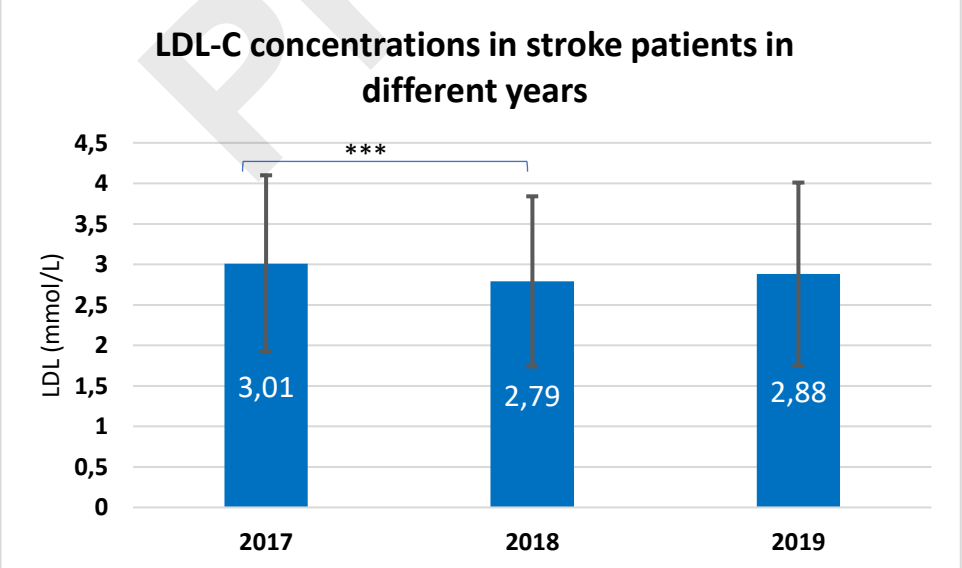

Fig. 2 Mean LDL-C concentrations (mmol/L) in stroke patients in different years after the initial diagnosis from all the obtained data from all specialists

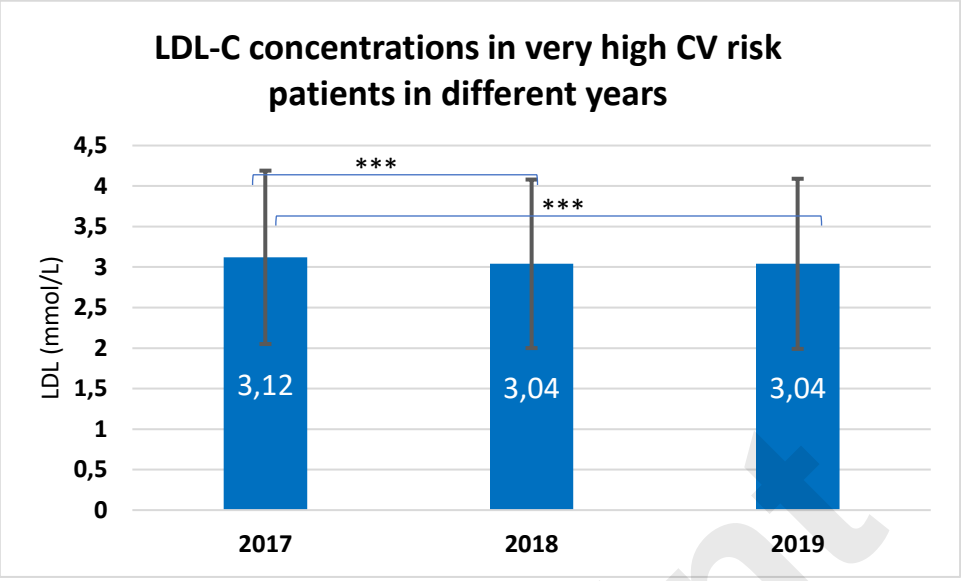

Fig. 3 Mean LDL-C concentrations (mmol/L) of patients in group 3 in each year after the initial diagnosis from all the obtained data from all specialists

Parameters monitored	Group 1 – patients with dg. ACS	Group 2 – patients with dg. CMP	Group 3 – Patients generally at high risk of CVD
Number of patients with LDL measurement each year	683	231	23 491
Average LDL values in 2017/2018/2019 (mmol/L)	3.29/3.06/3.04	3.16/3.01/3.12	3.30/3.21/3.18
LDL target attainment according to ESC/EAS 2016; years 2017/2018/2019 (%)	7.8% / 8.7% / 9.1%	7.8% / 8.7% / 9.1%	5.4% / 6.0% / 6.6%
LDL target attainment according to ESC/EAS 2019; years 2017/2018/2019 (%)	1.2% / 2.5% / 2.1%	1.7% / 1.7% / 2.6%	1.1% / 1.3% / 1.6%
Representation of patients with LDL ≥ 4.9 mmol/l (190 mg/dL)	9.1% / 6.9% / 6.0%	7.8% / 6.9% / 6.1%	8.3% / 6.7% / 6.5%

Attainment of the 2016 European Society of Cardiology/European Atherosclerosis Society guideline-recommended LDL-C targets

Tab. 2 Parameters monitored in individual patient groups with LDL measurement in each year

In the subgroup of ACS patients with LDL-C tests done each year (n=683), we found that only 6.9% (95% CI 5.1-9.1), 8.9% (95% CI 6.9-11.3), and 8.5% (95% CI 6.5-10.8) met the 2016 EAS/ESC-based LDL-C targets of LDL-C <1.8 mmol/L (< 70 mg/dL) in 2017, 2018, and 2019, respectively (Tab. 2; Fig. 4). In each year of follow-up, the largest proportion were ACS patients with measured LDL-C levels between 1.8 to 2.6 mmol/L (70 – 100 mg/dL). At the same time, the proportion of these patients is increasing year over year. Over the three years (2017-2019), the patients who had high (≥ 4.9 mmol/l; ≥ 190mg/dL) or higher (3.0 – 4.9 mmol/l; 115 – 190 mg/dL) measured LDL-C values at baseline (year 2017) were the most successful in lowering LDL-C (Fig. 5). **Patients with stroke** and LDL-C test done each year (n=231), only 7.8% (95% CI 4.7-12.0), 8.7% (95% CI 5.4-13.1), and 9.1% (95% CI 5.7-13.6) of patients met the target LDL-C values based on EAS/ESC 2016, 2017, 2018, and 2019, respectively (Tab. 2, Fig. 5). **Patients in very high CV risk group** with LDL-C test every year (n=23 491) had target values achieved in only 5.4% (95% CI 5.1-5.7), 6.0% (95% CI 5.7-6.4), and 6.6% (95% CI 6.3-6.9) of cases in each year of follow-up (Tab.1, Fig. 6).

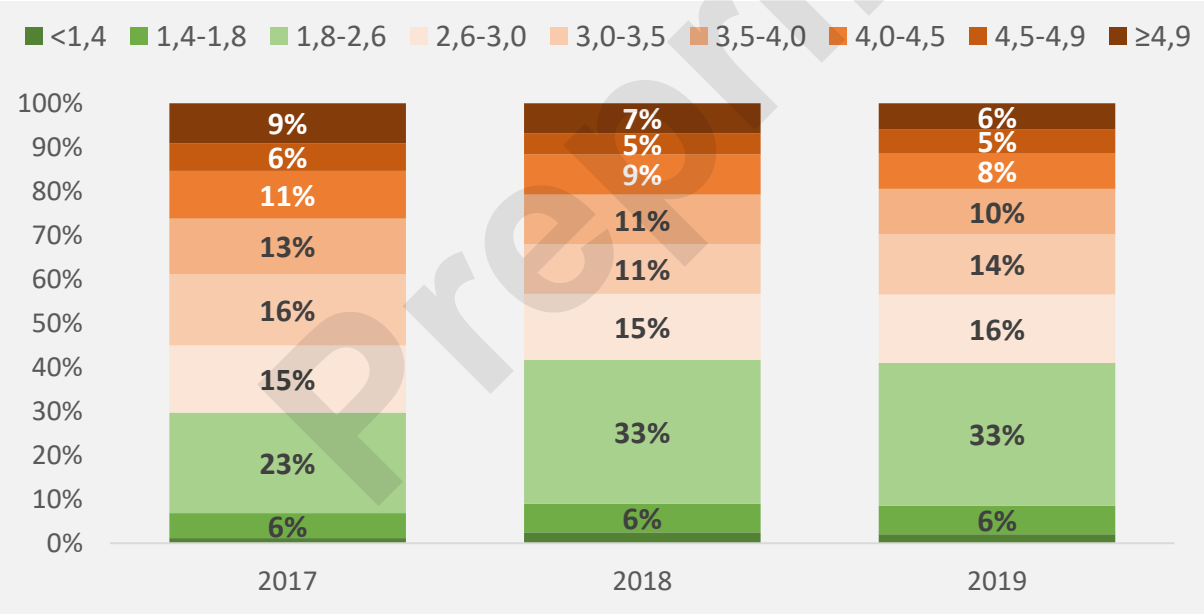

Fig. 4 Attainment of target LDL-C (mmol/L) values in 2017-2019 in the ACS subgroup of patients with LDL-C tests done each year (n=683)

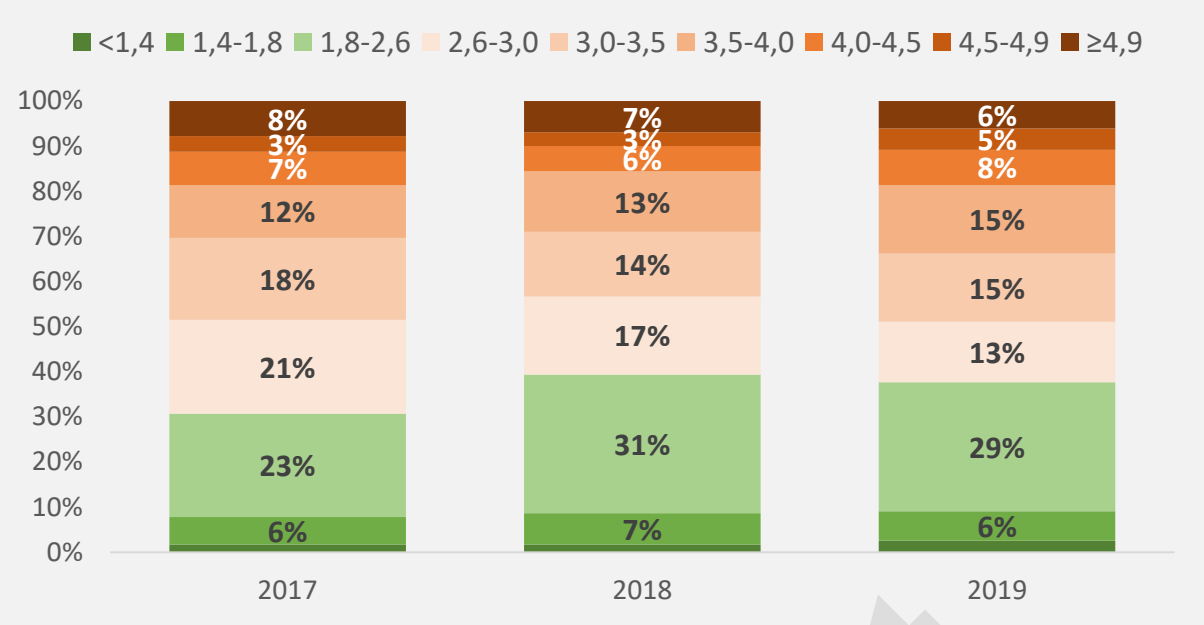

Fig. 5 Attainment of target LDL-C (mmol/L) values in 2017-2019 in group 2, in patients with dg. stroke with at least one examination in each year (n=231)

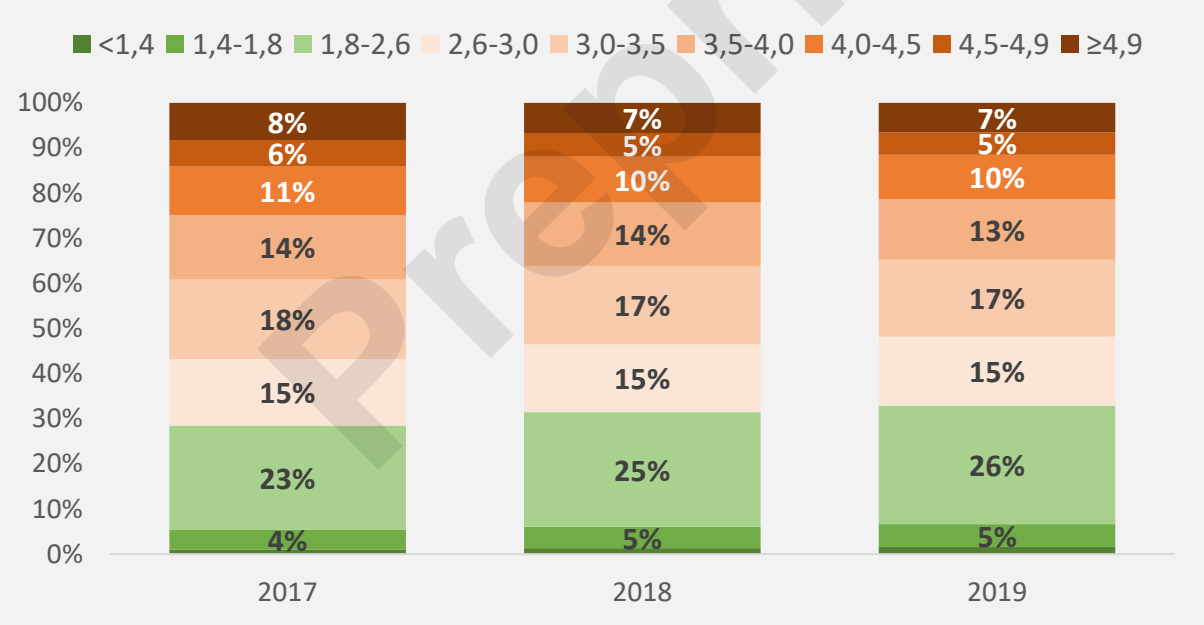

Fig. 6 Attainment of target LDL-C values (mmol/L) between years 2017-2019 in group 3, patients at very high CV risk, the subgroup of patients with LDL-C test done each year (n=23 491)

Attainment of the 2019 European Society of Cardiology/European Atherosclerosis Society guideline-recommended LDL-C targets

When analysing the data again using the new EAS/ESC 2019 recommendations, namely LDL-C <1.4 mmol/L (< 55 mg/dL), the target levels in the general population of patients at very high CV risk would be only 1.1% (95% CI 0.9-1.2), 1.3% (95% CI 1.2-1.5), 1.6% (95% CI 1.4-1.8) in years 2017, 2018, and 2019, respectively. For patients with ACS, this was 1.2% (95% CI 0.5-2.3), 2.5% (95% CI 1.5-4.0), and 2.1% (95% CI 1.1-3.4) of patients in 2017, 2018, and 2019, respectively. For patients in the stroke diagnosis group, LDL-C target levels were achieved by only 1.7% (95% CI 0.5-4.4), 1.7% (95% CI 0.5-4.4), and 2.6% (95% CI 1.0-5.6) of patients in the years 2017, 2018, 2019, respectively (Tab. 2).

Discussion

Globally, elevated levels of cholesterol and atherogenic lipoproteins are estimated to cause 2.6 million deaths per year and 29.7 million cases of decreased quality of life. Overall, up to 39% of women and 37% of men are thought to have total cholesterol levels above 5.0 mmol/L [9]. Large observational studies have shown that each 1 mmol/L LDL-C reduction leads to a 20-25% reduction in overall CV risk and a 20% reduction in coronary mortality [9,10].

Numerous international studies have been carried out that assessed the rate of attainment of target levels based on recommendations [11, 12, 13]. Most studies have focused on patients at very high, and high CV risk. Some have looked at recommendations' adherence and guideline patterns in very high-risk patients, such as those who have had a previous MI [14]. EUROASPIRE study examined primary and secondary prevention practices in patients diagnosed with coronary heart disease in Europe between 1995 and 1996, which had several follow-ups [15]. In EUROASPIRE IV from 2016, only 19.5% of patients with coronary artery disease had LDL-C levels below 1.8 mmol/L (70 mg/dl) [16]. Another study called The Dyslipidemia International Study (DYSIS) evaluated lipid abnormalities in relation to chronic statin therapy [17]. The first international dyslipidaemia study (DYSIS I), similarly to EUROASPIRE, found poor target attainment in very high-risk patients across Europe, ranging high values of 38.3% for the United Kingdom (UK) to low values of 9.2% for Greece [18]. DYSIS II study showed, that only 29.4% of patients with stable coronary artery disease achieved LDL target values below 1.8 mmol/L (70 mg/dl), and only 18.9% of patients with ACS achieved target LDL values [1]. The most recent survey (EUROASPIRE V) reports that target LDL-C < 1.8 mmol/L (70 mg/dl) was attained in less than 30% of patients surveyed. This percentage was slightly higher among patients on high intensity hypolipemic therapy [19]. A recent sub-analysis from EPHESUS study, a cross-sectional Turkish registry that enrolled patients with atherosclerotic disease, showed attainment of LDL-C targets in only 18% of cases [20]. LDL-C target attainment was even lower in a German cohort of patients with recent acute coronary syndrome enrolled in a retrospective registry. In this cohort, only 8.5% of patients with ASCVD achieved target levels [21]. Data from SAFEHEART registry in Spain showed that only 11.2% of patients with familial hypercholesterolaemia (FH) achieved target LDL-C levels [22]. Da VINCI study [23] described the success of achieving LDL-C target values and the most used hypolipemic agents. It was a cross-sectional observational study conducted in 18 countries including Slovakia with patients undergoing hypolipemic therapy as part of primary or secondary prevention. Only about half (54%) of all patients achieved target values based on

the 2016 primary prevention recommendations. For patients with ASCVD, this was only 30%. When applying the 2019 recommendations, only one-third (33%) of patients in primary prevention and only 18% with ASCVD reached target values [23]. The main pillar of CV disease prevention is risk factor modification. Based on the results of the IMPACT model, decreasing cholesterol is significant the most [24, 25, 26]. In Slovakia, compared to countries such as Poland, Hungary, the Czech Republic or Austria, this benefit is not fully utilised [27].

This retrospective study aimed to determine the attainment of recommended LDL-C levels in patients at very high risk, where proper management of risk factors is critical for the prevention of first or recurrent CV events. The analysis used data from 2017 to 2019, during which the 2016 ESC/EAS recommendations were in force [27]. Based on these recommendations, patients with documented cardiovascular disease, whether in the form of ACS, coronary revascularization (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or other arterial revascularization procedures, stroke, transient ischemic attack (TIA), peripheral arterial disease (PAD), are under very high cardiovascular risk. Previous studies have already pointed to the low degree of attainment of target LDL-C levels. The Dyslipidemia International Study (DYSIS I) Slovakia showed that the situation in attaining target LDL-C values in Slovakia is dire [29]. Among patients at very high CV risk, only 16.7% achieved the LDL-C ≤ 1.80 mmol/l target value (previous guidelines were in effect). Only 44.7% of subjects with documented CV disease had LDL-C between 1.81 and 2.90 mmol/l. Despite the existence of statin therapy and its widespread use, many patients still do not reach the target values. Similar results were obtained in the DYSIS II study, where target levels for very high cardiovascular risk (LDL-C ≤ 1.80 mmol/l, according to previous guidelines) were achieved by only 18.6% of patients [2]. Such small percentage is alarming, however in line with data from abroad. In the international DYSIS II study only 29.4% of patients achieved the target of ≤ 1.8 mmol/l LDL-C [1].

In our study, the results are even more disturbing. Among patients diagnosed with ACS, only 7-8% of patients achieved target LDL-C levels ≤ 1.80 mmol/l in each year of follow-up. Patients with stroke had values similar at 8-9%. When we included patients based only on the general ESC/EAS criteria for very high CV risk, these values were even lower at only 7%. We hypothesized that group 3, that is patients generally at very high CV risk, also included patients with manifested/diagnosed CCS. In these patients, LDL-C levels were not adequately controlled. In contrast, extremely high LDL-C levels above ≥ 4.9 mmol/l were present on average in 6-9% of patients at very high CV risk. The new 2019 ESC/EAS recommendations [5] have brought stricter target values and focused attention on intensified and combination

hypolipemic therapy. An important role was attributed to the results of meta-analyses confirming the dose-dependent reduction in ASCVD with LDL-C-lowering agents; the greater the absolute reduction in LDL-C, the greater the reduction in CV risk [5]. The benefits associated with LDL-C reduction are not specific only to statin therapy [30]. Furthermore, based on recent recommendations no lowest LDL-C level has been identified at which the risk outweighs the benefits. When re-analysing the data based on the latest recommendations, we arrive at an alarmingly low portion of patients (1-3%) who attain LDL-C target values of ≤ 1.40 mmol/l. However, this analysis is limited in part by the fact that older recommendations were still in effect in 2017, 2018, and up to September of 2019 so the data predicting the success in achieving of the target LDL-C according to the current guidelines need to be considered cautiously. Furthermore, the new recommendations dictate at least 50% reduction in LDL-C levels from baseline in addition to the overall decrease of ≤ 1.40 mmol/l. There has been a long-standing tendency in Slovakia to not prescribe the maximum tolerated dose of statins nor combination therapy, especially in the outpatient setting. The need to educate outpatient physicians in proper therapy utilisation, as well as the use of the latest therapeutic approaches is now even more essential [31]. This tendency was also confirmed in our study, where we monitored whether the changes in LDL-C in individual years were significant. During follow-up, we found that a significant decrease in LDL-C occurred in the second year of follow-up and subsequently this decrease was not significant in the next year. Moreover group 3 showed a slight increase. This also confirms the hypothesis that patients are initially administered more aggressive therapy in hospital settings or by specialists/cardiologists, but during outpatient management this therapy is subsequently down-titrated.

Extracting data from the Da VINCI study for Central and Eastern Europe, we find that countries in this region have 60% attainment in primary prevention based on the 2016 recommendations, 31% in secondary prevention, and 44% overall. Based on the 2019 recommendations, this is 24% overall, 37% in primary prevention and 13% in secondary prevention [32].

These differences between our study and the Da VINCI study [33] may have several explanations. The first is that our study was based on a retrospective analysis of large data set based on International Classification of Diseases (ICD) diagnoses. The benefit, in this case, is a large number of patients included. Da VINCI included 5 888 patients vs. 72 039 patients in our study. This difference may significantly affect the attainment of target LDL-C levels, as our data are from the whole country, without regional specificity, and without participating centre specificity. Therefore, bias which could be caused by using data from only specialised

centres where dyslipidaemia therapy tends be optimal, and not from outpatient clinics, where dyslipidaemia management may not be ideal, is not present without our dataset.

Our data are more coherent with the result of the recent large Santorini study [34], where it was found that up to 80% of high and very high-risk patients did not reach the target values from the 2019 ESC/EAS guidelines. Contributory factors may include CV risk underestimation and underutilization of combination therapies. Although our study was not aimed at monitoring the types of lipid-lowering therapies, it is generally known that the combined therapy of high-intensity statin and ezetimibe can decrease LDL-C by up to 65%, while the addition of the PCSK9 inhibitor can induce further reduction up to 85%. Our data suggest that most patients did have optimal medical therapy, however had extremely ineffective lipid-lowering therapy. In regular clinical practice, a patient is discharged after an acute cardiovascular event with a statin in the maximum dose, but a large percentage of patients require subsequent titration, which may be delayed in the outpatient setting, or patients are poorly monitored, and combined therapy is not used [34, 35].

We should follow the general rules highlighted in recent article [36], dictating that the earlier and longer therapy is key to better outcome for patients, and also to use combination therapy wherever possible. A recent study compared the stepwise approach and upfront combination therapy. Studies have shown that statin and ezetimibe combination therapy is superior to statin monotherapy in terms of significant reduction of all-cause mortality with an absolute risk reduction of 4.7% after 3 years. Similar results were highlighted in the RACING study, which showed that moderate-intensity statin with ezetimibe combination therapy was not inferior to high-intensity statin monotherapy among patients with ASCVD [37] and had higher degree of adherence compared to high-dose monotherapy. A certain benefit of early combined and intensified therapy could also be the achievement of LDL-C target values despite delayed visits to an outpatient cardiologist (which is not rare) in the early phases after initial cardiovascular event.

This study has some limitations which need to be acknowledged. Patients were classified based on their ICD diagnoses, which was the only method how patients were classified in high-risk CV disease group. It is possible that some high-risk patients were not included, or high-risk patients were wrongly classified into the very high-risk group. Also, our study monitors the situation only in Slovakia, which may differ considerably from other central or east European countries. Another limitation of this study is that the data were collected at the time when the 2016 guideline recommendations were in place, and the implementation of the 2019 guidelines is only illustrative, as the data are mostly from period before September 2019.

Attainment of goal LDL-C levels in Slovakia has been previously understudied despite having the highest CVD mortality and high CV risk factor rates compared with the rest of Europe. This study created a large dataset focused only on Slovakia and clearly illustrated the gap between recommended LDL-C goals and LDL-C levels in practice. The latest ESC/EAS recommendations, results of DYSIS I, II, and our study demonstrate the evident need for new therapeutic approaches and patient management recommendations in preventive cardiology. New and affordable hypolipemic agents with more favourable administration regimens would significantly improve patient adherence to therapy, improve outpatient management, and thus achieve better control and attainment of target LDL-C levels, reducing the incidence of new CV events.

Tab. 3 Attainment of target LDL-C in the mentioned observational studies

(more details, selection criteria in the text and in the mentioned publications [16, 18, 19, 20, 21, 22, 23, 32])

Study	Country	Number of observed patients	Attainment of target LDL-C valid in the years of the study
SlovakLipid	Slovakia	72 039	5%
EUROASPIRE IV [16]	24 European countries	16 426	19.5%
DYSIS II [18]	Belgium, France, Germany, Greece, Ireland, Italy Russia	880 ACS and 2778 CHD	ACS 23.2% CCS 29.6%
EUROASPIRE V [19]	27 countries in Europe	7824	30%
EPHESUS study [20]	Turkey	1868	18%
[21]	Germany	25 848 (ASCVD group)	8.5%
SAFEHEART [22]	Spain	4132 (HeFH)	11.2%
Da VINCI study [23]	14 European countries	9602	54% in primary prevention and 30% ASCVD (2016 guidelines) 33% in primary prevention, 18% with ASCVD (2019 guidelines)
Da VINCI study CEE [32]	Central and Eastern Europe (Czech Republic, Hungary, Poland, Romania, Slovakia, Ukraine	2154	60% in primary prevention and 31% in secondary prevention (2016 guidelines) 37% in primary prevention and 13% in secondary prevention (2019 guidelines)

Conclusion

Based on the results of this study, we concluded that patients at very high CV disease risk in Slovakia have poorly controlled atherogenic lipid levels and have LDL-C levels significantly higher than the recommended 1.8 mmol/L LDL-C for protection against adverse CV events, as per the then current ESC/EAS 2016 recommendations. Fewer than 5-10% of patients achieved the target levels in each risk group, which is significantly lower than the average in other countries globally (29.4%). These patients, despite adequate in-hospital management of ACS, stroke, and other CV diagnoses remain at high risk and are vulnerable to secondary CV events associated with inadequately controlled hyperlipidaemia. We hypothesize that patients at very high and high CV disease risk would benefit the most from intensified hypolipemic therapy.

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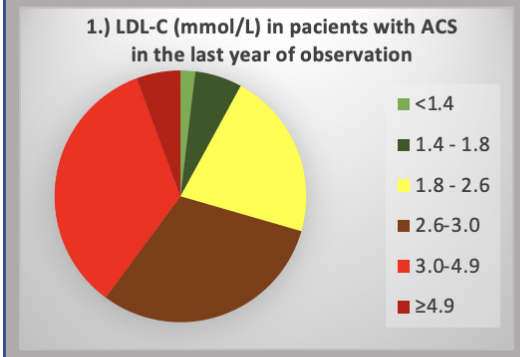
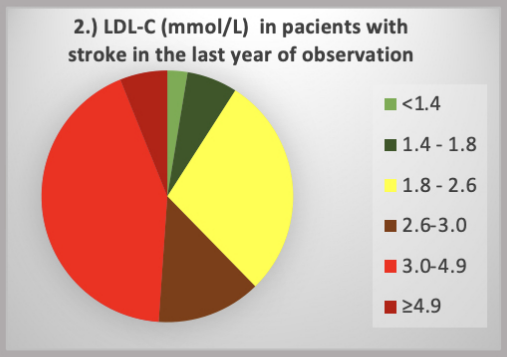
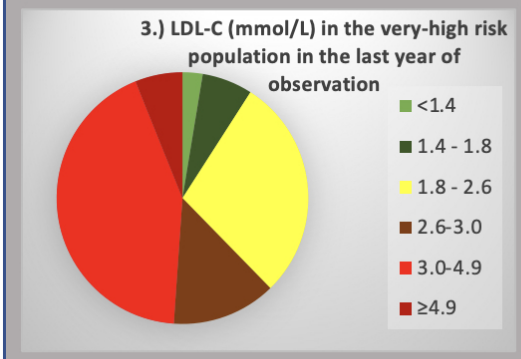
72 039 included very high-risk patients
220 657 LDL-C test results
3-year observation period

1.) Patients after the diagnosis AKS
2.) Patients after the diagnosis stroke
3.) Patients generally in the very high risk







- approximately 2% of patients in Slovakia reach the target LDL-C based on ESC/EAS 2019 guidelines; based on older guidelines it is 8%
- More than 6% of patients have LDL-C above ≥4.9 mmol/L
- Data could be applied also of other central and east European countries based on previous studies