Atherosclerosis 334 (2021) 66–75

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Lipid-lowering therapy use in primary and secondary care in Central and Eastern Europe: DA VINCI observational study

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ARTICLE INFO

Keywords:
Atherosclerosis
Cardiovascular
Dyslipidaemia
Low-density lipoprotein cholesterol

ABSTRACT

Background and aims: Central and Eastern Europe (CEE) is a largely understudied region, despite having the highest cardiovascular disease mortality in Europe. This analysis aimed to assess the proportion of patients in CEE who achieved their LDL-C goals based on individual cardiovascular risk recommended by the 2016 and 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines.
Methods: The DA VINCI study was a cross-sectional observational study of primary and secondary prevention patients receiving lipid-lowering therapy across Europe between June 2017 and November 2018.
Results: In total, 2154 patients were enrolled from the Czech Republic (n = 509), Hungary (n = 319), Poland (n = 460), Romania (n = 259), Slovakia (n = 123) and Ukraine (n = 484). At LDL-C measurement, most patients were on either moderate- or high-intensity statin monotherapy (53% and 32%, respectively). Despite this, only 44% of patients achieved risk-based LDL-C goals recommended by the 2016 ESC/EAS guidelines, ranging from 21% in Ukraine to 50% in Hungary and Romania. Only 24% of patients overall achieved the risk-based LDL-C goals recommended by the 2019 ESC/EAS guidelines, ranging from 11% in Ukraine to 32% in Poland.
Conclusions: Among patients receiving lipid-lowering therapy, more than half did not achieve their 2016 LDL-C goals. In one of the first comparative analyses evaluating 2019 risk-based goal attainment among countries in CEE, three-quarters of patients did not meet their 2019 LDL-C goals, highlighting a significant gap between guidelines and clinical practice for lipid management in CEE.

1. Introduction

Cardiovascular disease (CVD) remains the most common cause of mortality in Europe, resulting in more than 4 million deaths per year, and accounting for 45% of all mortality in this region [1]. Although Europe is commonly regarded as a single entity, it is comprised of different countries with diverse populations. Countries in Central and Eastern Europe (CEE), including the Czech Republic, Hungary, Poland, Romania, Slovakia and Ukraine, have the highest CVD mortality in Europe [2–4]. CVD death rates across countries in CEE are not only

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https://doi.org/10.1016/j.atherosclerosis.2021.08.035
Received 27 April 2021; Received in revised form 19 August 2021; Accepted 24 August 2021
Available online 25 August 2021
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higher than in other European countries, but they occur in individuals at a much younger age [2]. Despite this, CEE is understudied and data from this region are not often available. Available studies are primarily country-specific, which do not provide a holistic view of this region and very rarely provide comparative analyses [5]. This holds particularly true for the primary prevention population (i.e. patients without a history of a cardiovascular [CV] event), with studies focusing mainly on secondary prevention patients (i.e. patients with a confirmed history of CV events) [6].

Decades of research have shown that reducing low-density lipoprotein cholesterol (LDL-C) levels with statins lowers the risk of CVD and thus, statin therapy has become the mainstay of CVD treatment, particularly in patients with high or very high CV risk [7–10]. Lipid-lowering therapy (LLT) can be prescribed as monotherapy (statins alone) or as combination therapy such as statins with ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), as well as fibrates or omega-3 fatty acids [11–13]. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommend the use of statins as first-line treatment to lower LDL-C levels and subsequently reduce the risk of future CV events [3,14]. The ESC/EAS guidelines published in 2016 recommended LDL-C goals of less than 100 mg/dL [2.6 mmol/L] for those at high risk and less than 70 mg/dL [1.8 mmol/L] for those at very high risk. The updated ESC/EAS guidelines from 2019 went further and advocated for at least a 50% reduction in LDL-C from the untreated state in addition to lower, more stringent LDL-C goals (<70 mg/dL [1.8 mmol/L] and <55 mg/dL [1.4 mmol/L] for those at high and very high risk, respectively) [3,14].

This study aims to present contemporary data from the primary DA VINCI study for CEE, which is largely understudied, and evaluate whether primary and secondary prevention patients from CEE are achieving their risk-based LDL-C goals recommended by the ESC/EAS guidelines.

2. Patients and methods

2.1. Study design

The DA VINCI cross-sectional study consecutively enrolled 5888 adults (the primary analysis set), receiving LLT at primary and secondary care clinics across 18 European countries, between June 21, 2017 and November 20, 2018 [15]. Data for 2154 (37%) patients from six countries in CEE (the Czech Republic, Hungary, Poland, Romania, Slovakia and Ukraine) were extracted from the previously published DA VINCI study for this subgroup analysis. Other countries from CEE including Slovenia, Croatia and Bulgaria were not included in the study owing to logistical limitations and expected low recruitment rates. In addition, some of the countries initially invited to participate in the DA VINCI study were not included owing to lack of interest. Data for 287 (5%) patients from Northern European countries (Denmark and Sweden) and 2349 (40%) patients from Western European countries (Austria, Belgium, France, Germany, Greece, Ireland, Italy, Netherlands, Spain and United Kingdom), who participated in the DA VINCI study and had data evaluable to calculate goal attainment, were also extracted for this analysis. There were no formal study visits and patients were approached for participation at their routine clinic visits. Data were collected from medical records at a single enrolment visit, as detailed in the primary DA VINCI study report [15].

The study was designed by the Academic Executive Committee in conjunction with the sponsor, Amgen (full protocol available online [ENCePP; registration no. EU PAS 22075]). The study protocol was approved by the institutional review board or independent ethics committee from each site.

2.2. Eligibility criteria

Full eligibility criteria are available in the DA VINCI study report [15]. Briefly, major inclusion criteria included: being aged 18 years or older; providing informed consent; being prescribed LLT at enrolment or within 12 months before enrolment; and having an LDL-C measurement recorded up to 14 months before enrolment (obtained independently of participation in a clinical trial). Major exclusion criteria included: a diagnosis of familial hypercholesterolaemia (FH) with a history of CV events; comorbidities or personal circumstances that could affect clinical decision-making; a positive human immunodeficiency virus status; pregnancy or breastfeeding; participating in an interventional clinical trial within 6 months before enrolment; and a life expectancy of less than 1 year at enrolment.

2.3. Aims and outcomes

The primary outcome of the DA VINCI study was the proportion of patients achieving their LDL-C goals, based on individual CV risk, recommended by the 2016 ESC/EAS guidelines (2016 risk-based LDL-C goal attainment) while receiving stabilized LLT. This was assessed at LDL-C measurement, with stabilized LLT defined as no change in dose or regimen for at least 28 days before LDL-C measurement. Secondary outcomes were LLT use at enrolment and at LDL-C measurement.

Estimated 10-year CV risk at LDL-C measurement was established using the Systematic Coronary Risk Evaluation (SCORE) and Reduction of Atherosclerosis for Continued Health (REACH) tools in primary and secondary prevention groups, respectively, in accordance with the 2016 and 2019 ESC/EAS guidelines [16,17]. Individuals categorized as primary prevention patients at LDL-C measurement were further classified as low, moderate, high or very high risk, whereas those defined as secondary prevention patients were categorized as very high risk.

Because the study was completed before publication of the 2019 ESC/EAS guidelines, a *post hoc* analysis of the proportion of patients achieving their LDL-C goals, based on individual CV risk, recommended in the 2019 guidelines (2019 risk-based LDL-C goal attainment) was conducted for comparison.

The aim of this analysis was to describe how LLT is used for primary and secondary prevention of CVD within CEE and how this may affect LDL-C target goal attainment in countries in CEE.

2.4. Statistical analysis

All analyses were descriptive. Data were summarized for the overall CEE group and at country level, and separately for primary prevention and secondary prevention. Continuous variables are reported as mean and standard deviation (SD) or standard error (SE) for normally distributed data. For categorical variables, the number and percentage of patients in each category are reported.

3. Results

3.1. Patient characteristics

In total, 2154 patients were enrolled from six countries in CEE: 509 (24%) from the Czech Republic, 319 (15%) from Hungary, 460 (21%) from Poland, 259 (12%) from Romania, 123 (6%) from Slovakia and 484 (22%) from Ukraine. Patient characteristics at baseline are detailed in Table 1. The mean (SD) age of the overall CEE group was 64 (11) years, of whom 48% were women and 97% were White. The mean age and ethnicity of enrolled patients was similar across all countries.

In the overall CEE group, 81% of patients had hypertension, with no major differences among the different countries. The proportion of patients with diabetes mellitus was 38% in the overall group, which was similar across all countries; however, a larger proportion of Romanian patients had diabetes at baseline (62% [160/259]) compared with the other countries. Of note, there was a higher proportion of diabetes mellitus centres among the secondary care sites in Romania (50% [3/6]) than the other countries (Supplemental Fig. 1). The proportions of

Table 1
Baseline patient characteristics.

Characteristic	Czech Republic (n = 509)	Hungary (n = 319)	Poland (n = 460)	Romania (n = 259)	Slovakia (n = 123)	Ukraine (n = 484)	Overall CEE group (n = 2154)
Female	213 (42)	162 (51)	252 (55)	129 (50)	65 (53)	212 (44)	1033 (48)
Age (years), mean (SD)	67.7 (10)	65.5 (10)	64.2 (11)	63.4 (10)	64.1 (10)	60.5 (11)	64.3 (11)
White	473 (93)	310 (97)	459 (100)	252 (97)	122 (99)	475 (98)	2091 (97)
BMI (kg/m^2), median (Q1, Q3)	29 (26, 32)	28 (25, 32)	28 (25, 32)	30 (27, 34)	31 (28, 34)	29 (26, 32)	29 (26, 32)
Waist circumference (cm), mean (SD)	102 (13)	103 (14)	94 (13)	104 (13)	108 (11)	99 (11)	102 (13)
Hypertension	413 (81)	286 (90)	327 (71)	224 (86)	112 (91)	381 (79)	1743 (81)
Systolic blood pressure (mmHg), mean (SD)	135.2 (15)	129.3 (15)	130.5 (13)	138.7 (17)	133.7 (16)	139.9 (13)	134.7 (15)
Diastolic blood pressure (mmHg), mean (SD)	79.2 (10)	77.9 (10)	76.6 (10)	79.8 (10)	78.9 (9)	83.1 (9)	79.4 (10)
Diabetes mellitus	160 (31)	123 (39)	135 (29)	160 (62)	49 (40)	199 (41)	826 (38)
Fasting blood glucose[a] (mmol/L), median (Q1, Q3)	5.5 (5.0, 6.3)	5.9 (5.3, 7.1)	5.4 (4.9, 6.3)	6.6 (5.5, 8.3)	6.1 (5.3, 8.0)	6.0 (5.1, 7.9)	5.8 (5.1, 7.2)
Chronic kidney disease grade ≥3	25 (5)	7 (2)	23 (5)	16 (6)	4 (3)	12 (2)	87 (4)
Familial hypercholesterolaemia	8 (2)	0 (0)	1 (<1)	0 (0)	7 (6)	1 (<1)	17 (1)
Smoking history							
Non-smoker	287 (56)	209 (66)	240 (52)	186 (72)	91 (74)	262 (54)	1275 (59)
Ex-smoker	130 (26)	63 (20)	140 (30)	51 (20)	23 (19)	97 (20)	504 (23)
Light smoker	37 (7)	17 (5)	24 (5)	6 (2)	4 (3)	48 (10)	136 (6)
Moderate smoker	30 (6)	16 (5)	25 (5)	10 (4)	2 (2)	54 (11)	137 (6)
Heavy smoker	25 (5)	14 (4)	31 (7)	6 (2)	3 (2)	23 (5)	102 (5)
Vascular bed involvement							
Coronary	68 (13)	41 (13)	57 (12)	36 (14)	20 (16)	54 (11)	276 (13)
Cerebrovascular	118 (23)	82 (26)	88 (19)	41 (16)	19 (15)	126 (26)	474 (22)
Peripheral	95 (19)	66 (21)	35 (8)	38 (15)	25 (20)	115 (24)	374 (17)

BMI, body mass index; CEE, Central and Eastern Europe; Q, quartile; SD, standard deviation.
Data are presented as n (%) unless stated otherwise.
[a] Fasting blood glucose data were available for 1726 patients: 449 from Czech Republic, 321 from Hungary, 238 from Poland, 250 from Romania, 117 from Slovakia and 354 from Ukraine.

patients with comorbidities such as body mass index (BMI) above 30, waist circumference, chronic kidney disease, familial hypercholesterolaemia and a history of smoking were similar across all countries. Approximately half of the patients from the Czech Republic, Poland and Ukraine were smokers or ex-smokers.

3.2. CV risk profile

For primary prevention patients (n = 1173), the estimated 10-year CV risk was calculated using SCORE for 1166 patients (54%) (Fig. 1A). The majority were at moderate risk (60%), 29% were at high risk, 6% were at very high risk and 5% were at low risk. Ukraine and the Czech Republic had the highest proportions of patients who were categorized as having a very high CV risk (10% and 9%, respectively).

The REACH score could be estimated for 953 (44%) secondary prevention patients (n = 967) (Fig. 1B); approximately one-quarter of patients had a predicted 10-year risk of next CV event in the range of 20–30%. Most patients had a predicted 10-year risk that was greater than or equal to 30% (69%), ranging from 62% in Ukraine to 73% in Romania and Slovakia.

3.3. LLT patterns

LLT patterns, including the proportion of patients receiving statin as monotherapy or in combination with another therapy were assessed at enrolment and at LDL-C measurement (Table 2 and Supplemental Table 1). Of the patients in the overall CEE group who were receiving stabilized LLT and in whom LDL-C level could be assessed (n = 1476), 1360 (92%) received statins (Supplemental Table 1B). Moderate-intensity statin monotherapy was the most commonly prescribed treatment across all countries except for Slovakia, where high-intensity statin monotherapy was most commonly prescribed (Table 2). Of note, all of the enrolled patients from Slovakia were from secondary care sites (Supplemental Fig. 1). In the overall CEE group, 5% of patients were receiving ezetimibe in combination with moderate- or high-intensity statin and no patients were receiving PCSK9i. Almost one-tenth of patients in the Czech Republic and Hungary were receiving ezetimibe combination therapy (Table 2).

3.4. 2016 ESC/EAS guideline-recommended risk-based LDL-C goal attainment

Of the 1476 patients in the overall CEE group who were evaluable for LDL-C goal attainment, less than half (44%) achieved their risk-based 2016 LDL-C goals despite receiving stabilized LLT (Fig. 2A, i). At country level, approximately 50% of patients in the Czech, Hungarian, Polish and Romanian groups achieved their 2016 LDL-C goals. In Slovakia and Ukraine, 45% and 21% of patients achieved their 2016 LDL-C goals, respectively (Fig. 2A, ii). The majority of patients were receiving moderate- or high-intensity statin monotherapy (53% and 32%, respectively) and only 5% were receiving ezetimibe combination therapy (Fig. 2A, iii). Of note, 47% and 45% of patients who were treated with moderate- and high-intensity statin monotherapy, respectively, and 54% of those receiving ezetimibe combination therapy achieved their risk-based LDL-C goals (Fig. 2A, iv).

More than half of the primary prevention patients in the overall group (60%) achieved their 2016 risk-based goals (Fig. 2B, i), with attainment ranging from 35% in Ukraine to 67% in Romania (Fig. 2B, ii). The proportions of low-, moderate-, high- and very high risk primary prevention patients who achieved their LDL-C goals were 75%, 69%, 57% and 11%, respectively (Supplemental Fig. 2). Of the 812 patients in the secondary prevention group, the proportion of patients who attained their 2016 risk-based goals (31%) was half of that observed in the primary prevention group (Fig. 2C, i). Among the different countries, goal attainment in secondary prevention patients ranged from 15% to 38%: Hungary and Poland had the highest level of goal attainment (38%) and only 15% of patients from Ukraine reached their 2016 risk-based goals (Fig. 2C, ii). Within the secondary prevention subgroup, the highest proportions of patients who attained their 2016 LDL-C goals were those who were receiving ezetimibe combination therapy (53%) (Fig. 2C, iv).

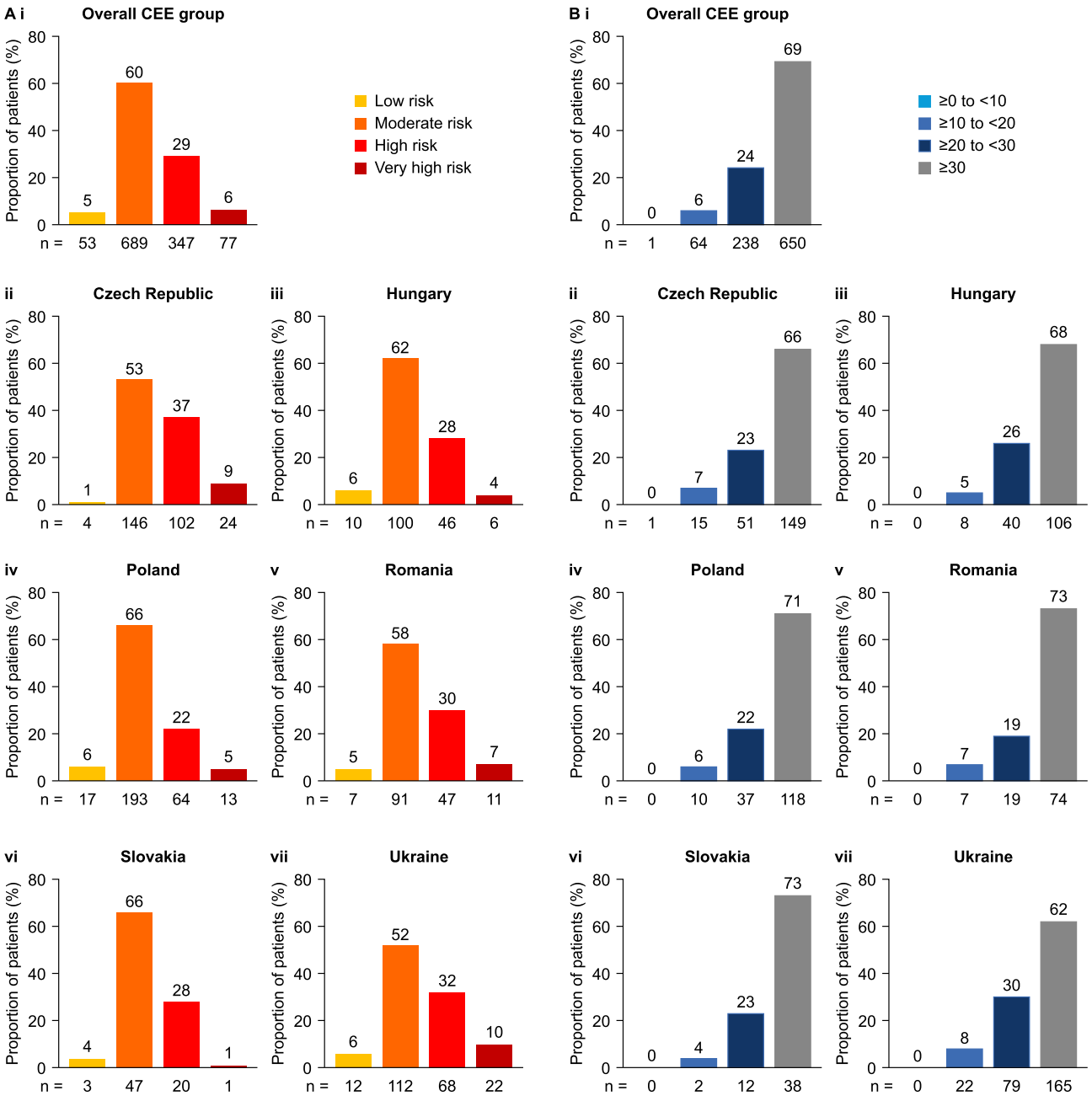


Fig. 1. Estimated ten-year CV risk at LDL-C measurement.
(A) Ten-year CV risk in the primary prevention group.[a,b] (B) Ten-year risk for next CV event in the secondary prevention group.[c,d] Of the 2154 participants from CEE, 1177 were categorized as primary prevention, 967 were classified as secondary prevention and 14 were categorized as other vascular secondary prevention (i.e having other evidence of atherosclerosis or other manifestation of vascular disease at enrolment). [a] Ten-year risk of CV death calculated using the SCORE tool. [b] SCORE could not be calculated for seven participants: one from the Czech Republic, four from Poland, one from Romania and one from Ukraine. [c] Ten-year risk for next CV event. [d] REACH scores could not be calculated for 14 participants: 11 from the Czech Republic, one from Hungary, one from Poland and one from Romania. CEE, Central and Eastern Europe; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; REACH, Reduction of Atherosclerosis for Continued Health; SCORE, Systematic Coronary Risk Evaluation.

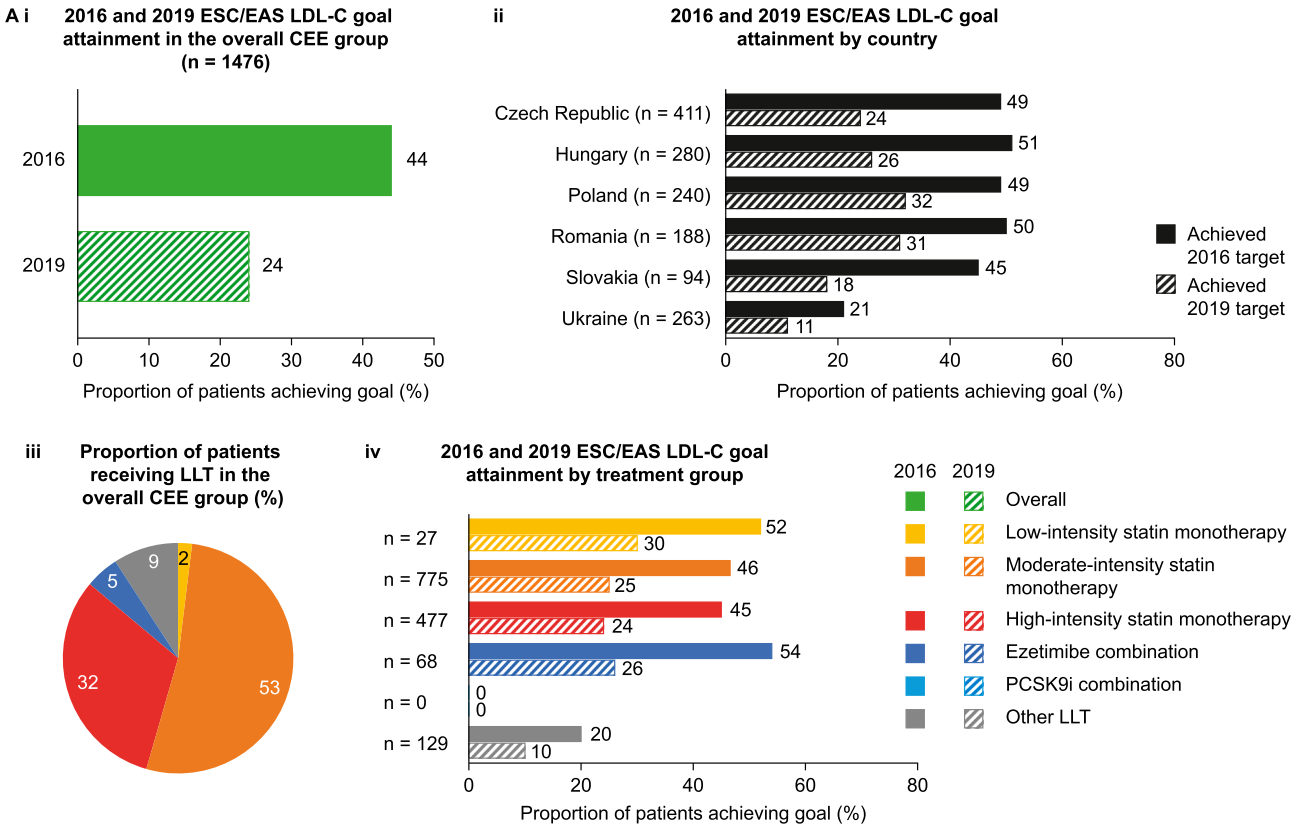
3.5. 2019 ESC/EAS guideline-recommended risk-based LDL-C goal attainment

In comparison with the 2016 risk-based LDL-C goal attainment, 2019 risk-based LDL-C goal attainment was lower in the overall CEE group as well as at country level (Fig. 2A). Approximately one-third of Polish and Romanian patients achieved their 2019 LDL-C goals. Only 24% of Czech patients, 26% of Hungarian patients, 18% of Slovakian patients and 11% of Ukrainian patients achieved their 2019 goals (Fig. 2A, ii). The proportion of patients who achieved their 2019 risk-based goals in the primary prevention group (37%) was lower than for 2016 goal attainment (60%) (Fig. 2B, i). Among primary prevention patients, only 19% and 4% of patients at high risk and very high risk, respectively, achieved their 2019 LDL-C goals (Supplemental Fig. 2). The proportion of secondary prevention patients who achieved their 2019 risk-based goals (13%) was lower than those who achieved their 2016 risk-based LDL-C goals (31%) (Fig. 2C, i).

Table 2
LLT use at enrolment and at LDL-C measurement.

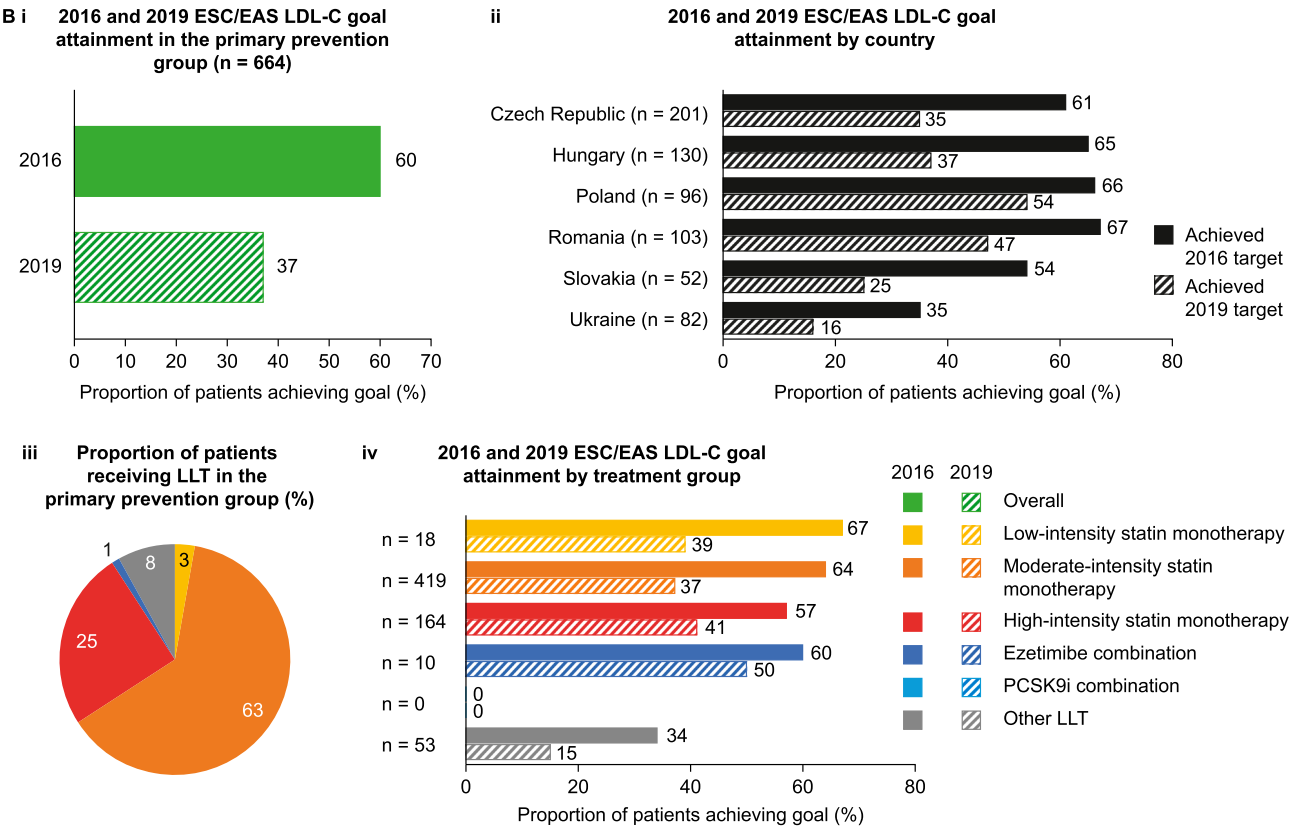
LLT use	Czech Republic	Hungary	Poland	Romania	Slovakia	Ukraine	Overall CEE group
LLT use at enrolment[a]							
n	509	319	460	259	123	484	2154
Low-intensity statin monotherapy	10 (2)	3 (1)	16 (3)	6 (2)	0 (0)	5 (1)	40 (2)
Moderate-intensity statin monotherapy	298 (59)	137 (43)	287 (62)	167 (64)	68 (55)	205 (42)	1162 (54)
High-intensity statin monotherapy	127 (25)	134 (42)	135 (29)	69 (27)	42 (34)	204 (42)	711 (33)
Ezetimibe combination therapy[c]	43 (8)	25 (8)	0 (0)	3 (1)	7 (6)	0 (0)	78 (4)
PCSK9i combination therapy[d]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other LLT[e]	31 (6)	20 (6)	22 (5)	14 (5)	6 (5)	70 (14)	163 (8)
LLT use at LDL-C measurement[b]							
n	411	280	240	188	94	263	1476
Low-intensity statin monotherapy	10 (2)	3 (1)	5 (2)	5 (3)	0 (0)	4 (2)	27 (2)
Moderate-intensity statin monotherapy	239 (58)	115 (41)	154 (64)	122 (65)	37 (39)	108 (41)	775 (53)
High-intensity statin monotherapy	106 (26)	120 (43)	71 (30)	49 (26)	38 (40)	93 (35)	477 (32)
Ezetimibe combination therapy[c]	35 (9)	25 (9)	0 (0)	2 (1)	6 (6)	0 (0)	68 (5)
PCSK9i combination therapy[d]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other LLT[e]	21 (5)	17 (6)	10 (4)	10 (5)	13 (14)	58 (22)	129 (9)

CEE, Central and Eastern Europe; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.
Data are presented as n (%) unless stated otherwise.
[a] Use of any LLT at enrolment or any LLT prescribed in the 12 months before enrolment.
[b] Stabilized LLT at LDL-C measurement.
[c] Ezetimibe plus statin of moderate, high or unknown intensity.
[d] PCSK9i plus a statin of low, moderate, high or unknown intensity; PCSK9i plus ezetimibe; or PCSK9i plus statin and ezetimibe.
[e] Ezetimibe without statin or PCSK9i; PCSK9i without statin or ezetimibe; ezetimibe plus statin of low or unknown intensity without ezetimibe or PCSK9i; or other LLTs such as fibrates or fish oils.



2016/2019 risk-based LDL-C targets: low risk, 2016/2019, <3.0 mmol/L (116 mg/dL); moderate risk, 2016, <3.0 mmol/L (116 mg/dL), 2019, <2.6 mmol/L (100 mg/dL); high risk, 2016, <2.6 mmol/L (100 mg/dL), 2019, <1.8 mmol/L (70 mg/dL); very high risk, 2016, <1.8 mmol/L (70 mg/dL), 2019, <1.4 mmol/L (54 mg/dL).

Fig. 2. Attainment of LDL-C goals recommended by the 2016 and 2019 ESC/EAS guidelines, by patient risk level and treatment regimen.
(A) Overall CEE group. (B) Primary prevention group. (C) Secondary prevention group. CEE, Central and Eastern Europe; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.



2016/2019 risk-based LDL-C targets: low risk, 2016/2019, <3.0 mmol/L (116 mg/dL); moderate risk, 2016, <3.0 mmol/L (116 mg/dL), 2019, <2.6 mmol/L (100 mg/dL); high risk, 2016, <2.6 mmol/L (100 mg/dL), 2019, <1.8 mmol/L (70 mg/dL); very high risk, 2016, <1.8 mmol/L (70 mg/dL), 2019, <1.4 mmol/L (54 mg/dL).

Fig. 2. (*continued*).

3.6. Mean LDL-C levels in patients with stabilized LLT

Among patients receiving stabilized LLT at the time of LDL-C measurement, the mean LDL-C levels were generally similar across Czech Republic, Hungary and Poland, ranging from 91 mg/dL (2.4 mmol/L) to 93 mg/dL (2.4 mmol/L). In Slovakia, mean LDL-C levels were 105 mg/dL (2.7 mmol/L) and in Ukraine, mean LDL-C was 118 mg/dL (3.1 mmol/L). The mean LDL-C level in the overall CEE group was 97 mg/dL (2.5 mmol/L) (Supplemental Fig. 3).

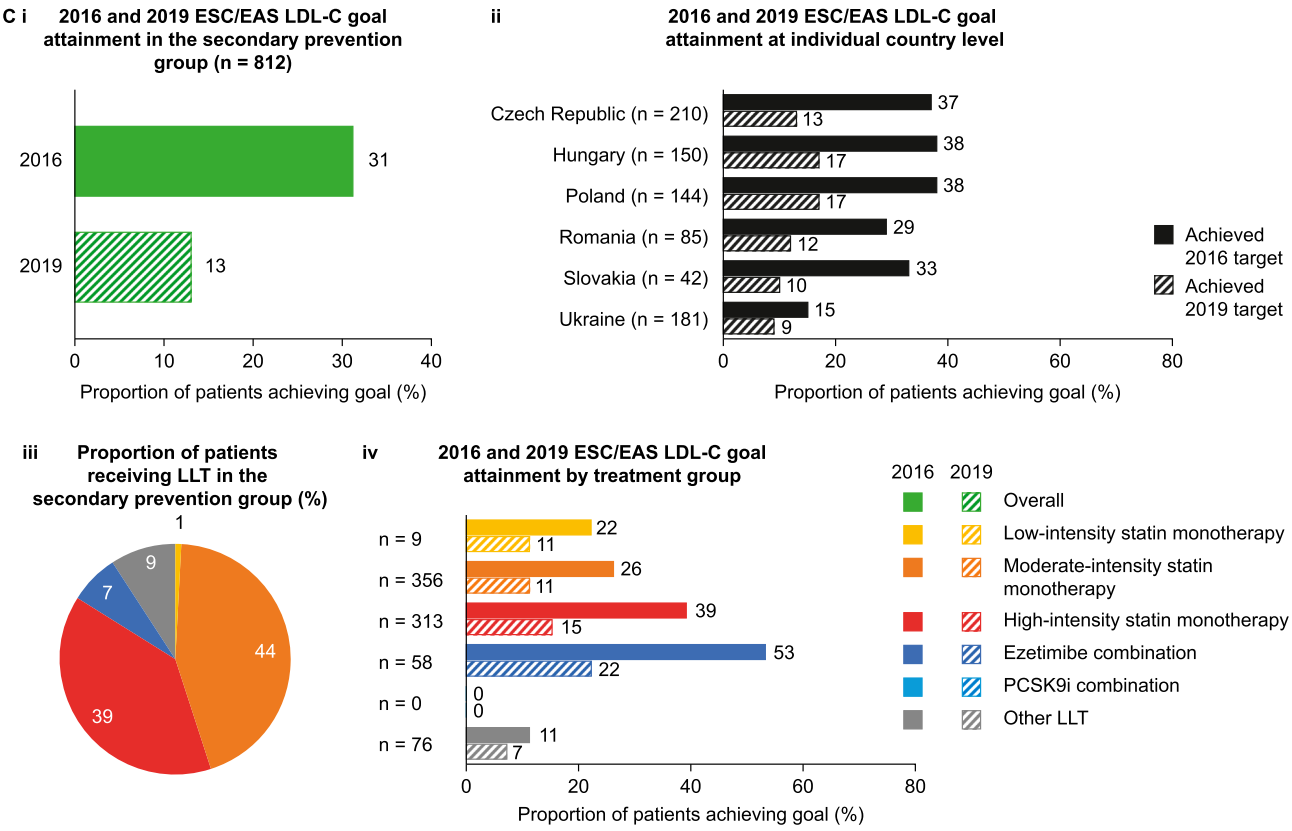
3.7. 2016 and 2019 risk-based LDL-C goal attainment in Western Europe, Northern Europe and CEE

Overall, risk-based LDL-C goal attainment was lower in CEE than in Northern Europe and Western Europe (Fig. 3). Among primary prevention patients, 60% achieved their 2016 LDL-C goals in CEE, which was a lower proportion than those who achieved LDL-C goals in Northern (73%) and Western (72%) Europe (Fig. 3A). Only 31% of secondary prevention patients in CEE achieved their 2016 risk-based LDL-C goals, whereas 44% and 45% achieved their 2016 LDL-C goals in Northern and Western Europe, respectively (Fig. 3A). Of note, only 13% of secondary prevention patients in the CEE countries achieved their 2019 LDL-C goals, compared with 23% in Northern and 22% in Western Europe (Fig. 3B).

4. Discussion

In this cross-sectional study of CEE, more than half of patients did not achieve their 2016 risk-based LDL-C goal and approximately three-quarters did not achieve their 2019 goal. To our knowledge, this is the first analysis to evaluate 2019 risk-based LDL-C goal attainment in CEE. Of all patients from CEE who were receiving stabilized LLT, 92% were receiving statins. Moderate-intensity statin monotherapy was the most common LLT regimen used. Despite this, approximately 70% of patients in Poland and Romania, 75% of patients in the Czech Republic, Hungary and Slovakia, and 90% of patients in Ukraine had LDL-C levels above those recommended by the 2019 ESC/EAS guidelines. Mean LDL-C levels in patients receiving stabilized LLT ranged from 91 mg/dL (2.3 mmol/L) in the Czech Republic to 118 mg/dL (3.1 mmol/L) in Ukraine, which were notably above the recommended LDL-C goals. LDL-C goal attainment was lower in CEE than in Northern and Western Europe. This study demonstrates a significant unmet need in CEE, with most primary and secondary prevention patients not achieving risk-based LDL-C goals recommended by the ESC/EAS guidelines. In addition, these findings indicate that CEE has the highest burden of dyslipidaemia compared with other European regions.

Marked differences in LDL-C goal attainment were observed among the different countries of CEE studied. For instance, the proportion of patients who achieved their 2016 LDL-C goals in Ukraine was low (21%) compared with Hungary and Romania (both 50%). A similar trend was observed with 2019 LDL-C goal attainment, which differed between countries and was lower than 2016 target attainment, ranging from 11% in Ukraine to 32% in Poland. These differences among countries in CEE may be because of differences in lifestyle, healthcare systems, socio-economic factors, varying availability of statins at all doses, special requirements for prescription (e.g., in some of the countries, only specialists can prescribe ezetimibe) and limited reimbursement programmes for LLT. Clinicians play an important role in lipid management [18,19]. When comparing results between different countries, the types of specialists in the participating sites of each country should be



2016/2019 risk-based LDL-C targets: low risk, 2016/2019, <3.0 mmol/L (116 mg/dL); moderate risk, 2016, <3.0 mmol/L (116 mg/dL), 2019, <2.6 mmol/L (100 mg/dL); high risk, 2016, <2.6 mmol/L (100 mg/dL), 2019, <1.8 mmol/L (70 mg/dL); very high risk, 2016, <1.8 mmol/L (70 mg/dL), 2019, <1.4 mmol/L (54 mg/dL).

Fig. 2. (*continued*).

considered. Specialists in internal medicine or neurologists may have had limited knowledge of LDL-C goals in the dyslipidaemia guidelines compared with lipidologists or cardiologists [19]. As such, depending on the clinicians' speciality, there may have been bias in the observed treatment patterns of LLT, consequently impacting LDL-C goal attainment. In this study, secondary care sites varied between countries. Slovakia had the highest proportion of participating secondary care sites, with most patients being treated by cardiologists (67%), whereas in Hungary only 29% of specialists were cardiologists.

Combination therapy is recommended in patients who are at high or very high CV risk, given that they are unlikely to achieve their 2019 LDL-C goals (<55 mg/dL [<1.4 mmol/L] or <40 mg/dL [< 1 mmol/L], respectively) with statins alone [20,21]. Furthermore, in selected secondary prevention patients, combination therapy is advised as early as possible during hospitalization to achieve 2019 LDL-C goals [22]. This study showed only 5% of patients from CEE received ezetimibe combination therapy and none were prescribed PCSK9i combination therapy. Combination therapies have not yet been widely adopted in CEE for several reasons such as limitations in reimbursement policies and pricing [20,23]. Significant limitations in reimbursement policies for PCSK9i and ezetimibe are the most important barrier to patients receiving highly effective LLT combinations in CEE [20,24]. For example, price variation among different statins and a lack of reimbursement for more potent statins (atorvastatin, rosuvastatin) as well as ezetimibe could be a reason for the remarkably low 2016 and 2019 LDL-C goal attainment observed in Ukraine (21% and 11%, respectively) [25]. A study assessing the cost-effectiveness of the 2016 ESC/EAS guidelines in patients with a history of CVD from EUROASPIRE IV, showed variations among estimated costs of statins and ezetimibe across different countries. In Czech Republic, the estimated costs for simvastatin were €0.04–0.29, which was relatively cheaper compared with Ukraine (€0.21–0.42) [26]. It is also noteworthy that following the expiry of the ezetimibe patent in 2017, cheaper generic versions have since become available in the EU. The lack of reimbursement for drugs coupled with low disposable incomes can result in restricted access to adequate treatments. Consequently, the limited access to combination therapies is likely to affect overall LDL-C goal attainment. Another possible reason for the low use of combination therapies in CEE is the limited availability of fixed dose statin-ezetimibe combinations at the time of this study. Biases in physician prescribing patterns are also a potential barrier to patients receiving adequate combination therapy. In this study, very high risk patients in the secondary prevention group were more likely to achieve their LDL-C goal compared with very high risk individuals from the primary prevention subgroup. This observation suggests that physicians may be biased towards underestimating the level of risk in patients without any history of CV event and can be reluctant to intensify LLT in these patients.

In line with our findings, the Hyperlipidaemia Therapy in Tertiary Cardiology Centre (TERCET) Registry study showed that 92% of patients with acute coronary syndrome in Poland were prescribed statins, with 38% receiving intensive statin therapy and approximately only 3% receiving combination therapy [27]. Similarly, longitudinal population data from the Czech Republic showed that statins were the most commonly prescribed regimen, with 79% of patients receiving statins in recent years [28]. Despite the availability of statins, recently published studies focusing on individual countries in CEE have highlighted the significant burden of dyslipidaemia in this region and the need for further action to achieve optimal LDL-C levels in CEE [29–33]. The LIPIDOGRAM studies are the largest population-based surveys assessing the prevalence of dyslipidaemia in Poland, which demonstrated that the

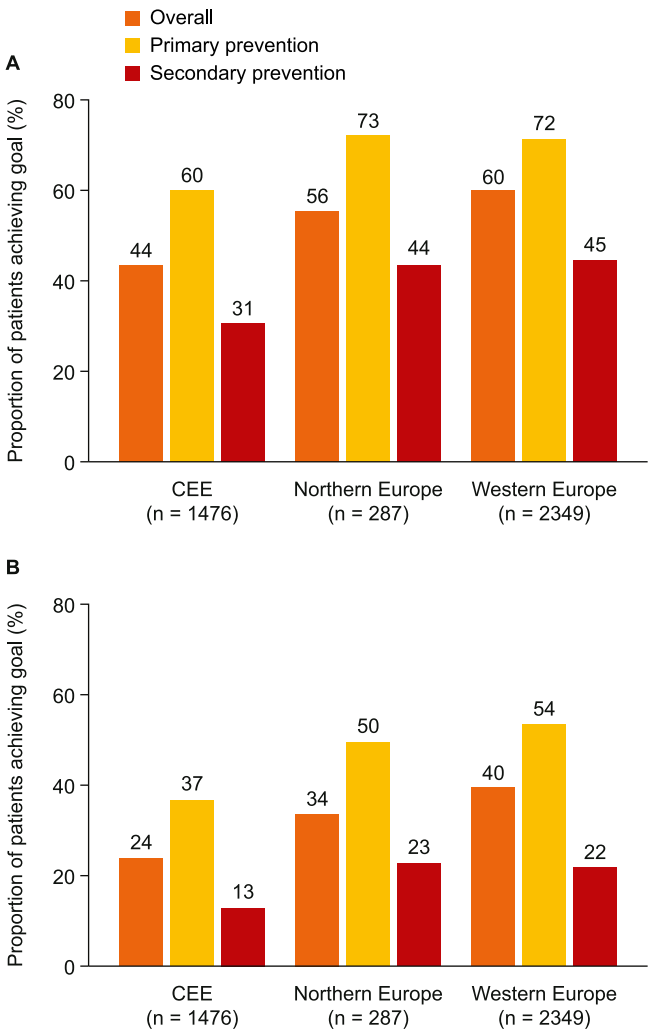


Fig. 3. Attainment of risk-based LDL-C goals recommended by the 2016 and 2019 ESC/EAS guidelines in CEE, Northern Europe and Western Europe.
(A) Attainment of risk-based LDL-C goals recommended by the 2016 ESC/EAS guidelines. (B) Attainment of risk-based LDL-C goals recommended by the 2019 ESC/EAS guidelines. CEE, Central and Eastern Europe; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol.

number of patients with dyslipidaemia in Poland remains high [29–31]. CV risk factors have also been shown to be elevated among Polish primary care patients. Of 13,724 Polish primary care patients enrolled in the LIPIDOGRAM2015 study, over 80% had dyslipidaemia, more than 60% had hypertension and more than 75% of patients were overweight or obese [32]. Similarly, a cross-sectional study of men and women from the primary care setting in Czech Republic showed a very high prevalence of dyslipidaemia (39% and 41%, respectively) [33]. Other contemporary population-based and cross-sectional studies have also included countries in CEE in their analyses and have highlighted the unmet need within this population [34,35]. In the SUrvey of Risk Factors study, an international clinical audit of 11 countries from Europe, Asia and the Middle East, 33% of patients in Europe achieved an LDL-C goal of less than 1.8 mmol/L [36]. EUROASPIRE III was a large cross-sectional survey conducted in 2006–2007, which showed that 55% of patients did not reach their LDL-C goal of less than or equal to 97 mg/dL (2.5 mmol/L) [37]. Similarly, EUROASPIRE IV, carried out between 2012 and 2013, showed that 58% and 19% achieved their LDL-C targets at the time of the study (<97 mg/dL [2.5 mmol/L] and <70 mg/dL [1.8 mmol/L], respectively) [38]. The EUROASPIRE V study demonstrated that 2016 LDL-C goal attainment in patients from CEE, among others, is low, and this is likely to be reduced with the more stringent 2019 ESC/EAS LDL-C goal recommendations [39–41]. Indeed, in our study, the proportion of patients who achieved their 2019 LDL-C goals was markedly lower (24%) in CEE countries than in European countries included in EUROASPIRE, reinforcing the burden of dyslipidaemias in this region.

This study has some limitations which need to be acknowledged. A planned sample size was chosen to allow each individual country to be represented with a minimum of 200–300 patients, which would allow precise estimates of the primary outcome measure (LDL-C goal attainment) within each country [15]. As a result, the number of study sites and patients enrolled per country were not stratified according to the population of each country. In addition, the sample sizes of the treatment groups may limit the interpretation of the results presented. Owing to the small sample sizes, the secondary prevention group was not evaluated by vascular bed involvement. From the total number of patients enrolled, not all had evaluable data at LDL-C measurement resulting in a reduction of the total sample size. Furthermore, it should be noted that although PCSK9i were available for reimbursement in some of the countries at the time of study, the use of PCSK9i was very limited and largely restricted by country-specific reimbursement criteria. Finally, as with all registries, the sites that participated were likely those which focused on lipid management and therefore, the findings of this study reflect a 'best-case scenario' which may not be representative of patients in other regions.

This is one of the largest data sets of this kind from CEE, which has been previously understudied despite having the highest CVD mortality and high CV risk factor rates compared with the rest of Europe [2]. This study sheds light on the gap between the recommended LDL-C goals and the LDL-C levels that are achieved in clinical practice in CEE, despite the use of statin monotherapy in most of the population. This misalignment may be because of non-adherence to medication by the patient, lack of familiarity among physicians with the ESC/EAS recommendations, prescription of non-optimal doses of statin monotherapy, access to more potent LLT and very limited use of combination therapies. These findings highlight the need for government and policy-makers in CEE to drive change in current clinical practices for the management of CVD. Here, we suggest several key solutions to improve low LDL-C goal attainment in countries in CEE: (1) implementation of improved reimbursement strategies that provide clinicians with full access to statins at all doses and ezetimibe, enabling clinicians to decide which group of patients might benefit the most from innovative therapies (PCSK9i and recently approved bempedoic acid and inclisiran); (2) further education for healthcare professionals, including general practitioners, endocrinologists, cardiologists, interventional cardiologists and lipidologists and patient organizations, to increase awareness regarding the importance of dyslipidaemia in CVD and mortality; (3) increased support of national and international societies such as the EAS and the International Lipid Expert Panel (ILEP), which would be critically important when discussing reimbursement criteria with payers and for sharing best practices. The implementation of these changes would lead to increased awareness among healthcare practitioners and patients about the dyslipidaemia burden in CEE and encourage combination therapy use in everyday clinical practice to achieve LDL-C goals and reduce CVD risk.

These analyses demonstrate that among patients receiving LLT, more than half of patients did not achieve their 2016 LDL-C risk-based goals. In one of the first analyses of 2019 risk-based LDL-C goal attainment in CEE, three-quarters of patients did not achieve their goals. The results from this study highlight a significant unmet need and indicate a need for policy-makers to drive change in clinical practices for lipid management in countries in CEE.

Financial support

This work was supported by Amgen GmbH.

Author contributions

MV, MB contributed substantially to the sub-study design and concept; MV, MB, JJJ, AP, DG, KR, RGK were involved in data acquisition; SB conducted the data analyses; and all authors assisted with interpretation of the data. KKR conceived, designed, secured funding and supervised the overall DA VINCI study. All authors were involved in drafting of the manuscript, provided critical revisions for important intellectual content, approved the final version submitted for publication, and agreed to be accountable for all aspects of the work.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MB is on the speakers' bureau for Akcea, Amgen, Daiichi Sankyo, KRKA, MSD, Mylan, Polpharma, Sanofi-Aventis, Servier and Valeant; is a consultant to Abbott Vascular, Akcea, Amgen, Daiichi Sankyo, Esperion, Freia Pharmaceuticals, MSD, Polfarmex, Resverlogix and Sanofi-Aventis; and reports grants from Mylan, Sanofi and Valeant. JJJ reports a research grant/support from Valeant and has served as a consultant or speaker for ALAB Laboratories, Amgen, Bioton, Boehringer Ingelheim, Celgene, Microlife, Servier, Teva and Valeant. DG reports fees for educational activities from Amgen, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Merck, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi and Servier. KR reports fees for clinical trials, consultancy and presentations from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Gilead, Merck, Mylan, Novo Nordisk, Pfizer, Sanofi and Zentiva. KKR reports a grant from Amgen during the conduct of the study, and personal fees from AbbVie, Aegerion, Akcea, Algorithm, AstraZeneca, Bayer, Boehringer Ingelheim, Cerenis, Cipla, Dr Reddy's, Esperion, Kowa, Lilly, The Medicines Company, Novartis, Silence Therapeutics, Takeda and Zuellig Pharma, and grants and personal fees from Amgen, Daiichi Sankyo, MSD, Pfizer and Sanofi/Regeneron, outside the submitted work. MV reports fees for clinical trials, consultancy and presentations from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Mylan, Novartis, Novo Nordisk, Sanofi and Zentiva. AP reports grants from Sanofi/Regeneron, Amgen and Esperion, and personal fees from Servier, Bayer, AstraZeneca, Boehringer Ingelheim, Novo Nordisk and Aspen. MZ is an employee of Amgen.

Acknowledgements

The authors would like to thank all the patients who participated in this study as well as Natasha Rangwani, PhD, of PharmaGenesis London, London, UK, for medical writing support. The authors would like to acknowledge Dr Gaia Kiru, Dr Jennifer Murphy and Mrs Amanda Bravery from Imperial College London for the additional support provided. KKR also acknowledges the support provided by NIHR Imperial Biomedical Research Centre and NIHR ARC for Northwest London.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.08.035.

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