Clinical Management of High and Very High Risk Patients with Hyperlipidaemia in Central and Eastern Europe: An Observational Study

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ABSTRACT

Introduction: A retrospective/prospective observational study was conducted to explore the current management of hyperlipidaemia in high-risk (HR) and very high risk (VHR) patients in central/eastern Europe and Israel.

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Methods: The study enrolled adult patients who were receiving lipid-lowering therapy and attending a specialist (cardiologist/diabetologist/lipidologist) or internist for a routine visit at 57 sites (including academic/specialist/internal medicine centres) across Bulgaria, Croatia, Czech Republic, Israel, Poland, Romania and Slovakia. Data were collected from medical records, for the 12 months before enrolment, with/without ≤ 6 months' additional prospective follow-up.

Results: A total of 1244 patients, mean (SD) age 63.3 (11.3) years were included (307 with familial hypercholesterolaemia (FH), 943 secondary prevention patients). Almost all patients (98.1%) were receiving statins (76.7% monotherapy/21.4% combined therapy), with

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53.1% receiving high-intensity statin therapy: 127 patients (10.2%) had adverse events attributed to statin intolerance. Mean (SD) low density lipoprotein cholesterol (LDL-C) levels were 3.3 (1.7) mmol/L at the first, and 2.7 (1.3) mmol/L at the last, visit of the retrospective phase of observation, with little change during the prospective phase. Less than one-quarter (23.8%; 95% CI 17.29–31.45%) of HR patients and less than half (42.0%; 39.05–44.98%) of VHR patients achieved their risk-based LDL-C targets of < 2.5 and < 1.8 mmol/L, respectively. Less than 15% of FH patients reached these targets (10.9% (5.6–18.7%) of HR and 12.1% (8.0–17.4%) of VHR patients). The revised 2016 ESC/EAS target for HR patients (2.6 mmol/L) was met by 28.5% (21.44–36.38%) of HR patients overall. Almost one-half of patients (42.1%) experienced one or more cardiovascular events during observation.

Conclusion: Our findings confirm that, despite widespread statin use, a substantial proportion of patients treated for hyperlipidaemia in central/eastern Europe and Israel, particularly those with FH, do not reach recommended LDL-C targets, thus remaining at risk of cardiovascular events.

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Keywords: Cardiology; Cardiovascular events; Hyperlipidaemia; Low-density lipoprotein cholesterol

INTRODUCTION

Hyperlipidaemia is a major modifiable risk factor for the development of cardiovascular (CV) disease, the leading cause of death and disability in the developed world [1]. It is estimated that up to 50% of the European population in the 35–64 years age bracket has total cholesterol level > 6.5 mmol/L [2]. A large body of data from both primary and secondary prevention settings demonstrate that reducing elevated total cholesterol, non-high-density lipoprotein cholesterol (non HDL-C), and most importantly low density lipoprotein cholesterol (LDL-C), via lipid-modifying treatment (LMT), lowers the risk of CV events [3–5]. Moreover, the degree of risk reduction is proportional to the LDL-C

reduction. A meta-analysis of 21 randomised controlled trials of statin therapy in almost 170,000 patients indicated that for every ~ 1 mmol/L reduction in LDL-C the risk of major vascular events is reduced by ~ 20% over a period of approximately 5 years [6].

Guidelines from the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) emphasise the importance of setting clear LDL-C targets for patients with hyperlipidaemia and using aggressive LMT to achieve these [7, 8]. In 2011 the guidelines recommended an LDL-C goal of < 2.5 mmol/L (96.5 mg/dL) for high-risk (HR) patients and < 1.8 mmol/L (70 mg/dL) for very high risk (VHR) patients. The target for HR patients was subsequently revised to < 2.6 mmol/L (100 mg/dL) in 2016 [8]. Statin therapy has been the mainstay of hyperlipidaemia treatment for several decades. Guidelines recommend administration of the highest tolerated statin dose until the LDL-C target is met, with the addition of non-statin treatment(s) for patients failing to reach target with statin monotherapy [7, 8].

Most of the literature on LMT use and lipid control comes from 'Western' countries such as the USA and western Europe, with corresponding data from central and eastern European populations being much more limited, reflecting a lack of patient registries and access to public/health insurance data in eastern Europe. Rates of CV morbidity and mortality are generally much higher in eastern Europe than in western Europe [9], with 2015 data indicating that Lithuania had the highest standardized death rate for ischaemic heart disease in the European Union (760 per 100,000 male residents), followed by Latvia, Hungary, Slovakia, the Czech Republic and Romania (395–600 per 100,000 male residents, cf. 77/100,000 in France) [10]. Thus, it is important to obtain more data from patients receiving hyperlipidaemia treatment in this region.

Accordingly, we conducted an observational study with the aim of gaining insight into the current management of hyperlipidaemia and LDL-C target achievement in HR and VHR patients in Bulgaria, Croatia, Czech Republic, Poland, Romania, Slovenia and Slovakia, as well as Israel.

METHODS

Study Population

This retrospective/prospective observational study enrolled adult patients with hyperlipidaemia (HR or VHR as defined by 2011 ESC/EAS guidelines) [7] who were receiving LMT and attending a specialist (cardiologist/diabetologist/lipidologist) and/or internist for a routine visit during the enrolment period. They were required to have ≥ 2 recorded LDL-C values and valid LMT documentation (type of medication and dose) for the retrospective data collection period. Patients receiving treatment for hyperlipidaemia within the course of an interventional clinical trial were excluded. All patients participating in the prospective phase were required to have all LDL-C and corresponding LMT data for this period.

Study Conduct

In order to enrol a representative patient population in the study, we included academic and non-academic centres, specialised clinics and internal medicine clinics. The study enrolled all eligible subjects who provided informed consent (as applicable per respective country legislation) from the participating sites.

Data were collected from individual patient medical records, for the 12 months prior to enrolment (retrospective phase) and ≤ 6 months following enrolment in the three countries participating in the prospective phase (Romania, Poland, Czech Republic).

Ethics/Consent

There were no study-related medical procedures undertaken. The study was conducted in accordance with the Helsinki Declaration of 1964, as revised in 2013, and with country-specific legal and regulatory requirements. It was approved by ethics committees and for registration or classification by regulatory bodies, as applicable in each country:

1. Bulgaria: Republic of Bulgaria Ministry of Health Ethics Committee for Multicentre Trial,

Sofia; 2. Croatia: Agency for Medicinal Products and Medical Products Central Ethics Trust, Zagreb; 3. Czech Republic: Ethics Committee of: Faculty Hospital Hradec Králové, Králové; Institute for Clinical and Experimental Medicine (IKEM) and Thomayer Hospital, Prague; Faculty Hospital Brno, Brno; Faculty Hospital Plzeň, Plzeň; General Teaching Hospital in Prague, Prague; St. Anne's Faculty Hospital in Brno, Brno; Ethics Committee for Multicentre Clinical Assessment of the Motol University Hospital, Prague; Pardubice Regional Hospital Svitavska Hospital 4. Israel: Helsinki Committees of: Edith Wolfson Medical Centre, Tel Aviv; Chaim Sheba Medical Center, Tel Hashomer; Hadassah Medical Center, Jerusalem; Rabin Medical Center, Petah Tikva; Lady Davis Carmel Medical Center, Haifa; Soroka Medical Center, Beersheba; Bnai Zion Medical Center, Haifa; Meir Medical Center, Kfar Saba; Ziv Medical Center, Safed. 5. Poland: Bioethical Commission in Kielce at the Świętokrzyska Medical Chamber. 6. Romania: Romania Medical Sciences Academy, National Bioethics Committee for Medicines and Medical Devices, Bucharest. 7. Slovakia: Multicentre Ethics Committee of Kosice Self-Governing Region, Kosice.

The study followed generally accepted research practices described in Good Epidemiological Practice guidelines issued by the International Epidemiological Association. All data were handled in strictest confidence in conformity with national and European data protection regulations (such as Directive 95/46/EC). All patients provided written informed consent, where required by local regulations.

Objectives

The primary study objective was to estimate the proportion of patients achieving LDL-C levels of < 2.5 mmol/L and < 1.8 mmol/L, the ESC/EAS-defined target levels at the time for HR and VHR patients, respectively [7]. We also included the revised 2016 target of < 2.6 mmol/L for HR patients [8] in our analysis. Secondary objectives included LDL-C levels over time; use of statins/other LMT (type, dose, frequency) over time; patient clinical characteristics

(demographics, medical history including familial hypercholesterolaemia (FH) diagnosis, statin intolerance symptoms (as recorded by the investigators on the case report form), CV events and hospitalisations).

The definition of statin intolerance is a matter of debate. For instance it has been defined by an International Lipid Expert Panel as 'the inability to tolerate at least two statins: one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal laboratory determinations, which are temporally related to statin treatment and reversible upon statin discontinuation' [11]. However in this report the term statin intolerance simply refers to adverse events that were attributed to statin intolerance (partial or complete). CV events included coronary heart disease (unstable angina pectoris/myocardial infarction/sudden cardiac death), cerebrovascular disease (transient ischaemic attack/stroke) or peripheral artery disease (intermittent claudication/ischaemic rest pain/gangrene/abdominal aortic aneurysm/atrial fibrillation/heart failure/coronary revascularisation). Patients' CV risk was categorised according to physician evaluation. No formal hypothesis was tested.

Study Sample Size

In order to enable sufficiently precise estimates of the primary outcome measure (achievement of ESC/EAS LDL-C targets) to be calculated for each country, it was planned to enrol approximately 1300 subjects in total across eight countries, with each country enrolling between 80 and 150 subjects. Assuming that 50% of subjects achieve the target, a sample size of 80 patients would enable the percentage to be estimated with a 95% confidence interval (CI) with a half-width of 11.0%, while a sample size of 150 patients would result in a half-width of 8.0%.

Data Analysis

Summary statistics only are presented. For categorical variables, including the primary outcome measure, the frequency and percentage in category, with 95% CI, were calculated. For continuous variables the number of subjects, mean, median, standard deviation or standard error, 25th and 75th percentile (Q1, Q3), minimum and maximum are presented. There was no imputation for missing data.

LDL-C levels were analysed by patient subgroups of interest: FH, secondary prevention, diabetic, ST-segment elevation myocardial infarction (STEMI) and statin intolerant (SI; see "Methods" section), as noted on the case report form. A post hoc analysis was conducted, comparing last-visit LDL-C levels for each subgroup with values for all other patients, using the nonparametric Mann–Whitney U test.

For countries with retrospective and prospective data collection, the retrospective and prospective data were combined in the primary endpoint analysis. The two portions of data were also summarised separately, to evaluate any differences in terms of data quality and completion.

RESULTS

Study Population

A total of 1281 patients were enrolled at 57 sites, in Romania (n = 239: 10 centres); Bulgaria (234: 8); Czech Republic (209: 11); Israel (205: 9); Poland (152: 6), Slovakia (152: 9) and Croatia (90: 4). The Slovenian centres did not participate because of delayed regulatory approval and this led to higher patient accrual rates in the other countries. Most sites were cardiology or diabetology/lipidology clinics: only the Czech and Slovak Republics included internal medicine clinics.

Thirty-seven patients were found to be ineligible and excluded from study participation, leaving 1244 patients who were followed retrospectively, with 585 also followed prospectively, between January 2015 and March 2017. Only seven patients discontinued study participation, due to death (4 patients), loss to follow-up (2) or subject decision (1) (Table S1; in electronic supplementary files).

Table 1 Characteristics of the study population (n = 1244)

Parameter	Category/statistic	
Male/female	n/n	787/457
Age (years)	Mean (SD)	63.3 (11.28)
	Median (Q1–Q3)	64.0 (58.0–71.0)
	Range	18–92
Body weight (kg)	Mean (SD)	84.5 (16.59)
	Median (Q1–Q3)	83.0 (73.5–94.0)
	Range	42–173
Time since diagnosis[a]	< 1 year	220 (17.7%)
	≥ 1 and < 2 years	81 (6.5%)
	≥ 2 and < 5 years	131 (10.5%)
	≥ 5 years	534 (42.9%)
	Unknown	278 (22.3%)
Subgroup	FH	307 (24.7%)
	Secondary prevention	943 (75.8%)
	Diabetes	528 (42.4%)
	STEMI	208 (16.7%)
	Statin intolerant[b]	127 (10.2%)
DLCN score (FH patients)	< 3	51 (16.3%)
	3–5	86 (27.5%)
	6–7	86 (27.5%)
	≥ 8	84 (26.8%)
CV risk	High	151 (12.1%)
	Very high	1093 (87.9%)

DLCN Dutch Lipid Clinic Network criteria [12]: definite/probable FH ≥ 6; possible FH 3–5; unlikely FH < 3; *FH* Familial hypercholesterolaemia; *STEMI* ST-Elevation Myocardial Infarction

[a] Diagnosis of hyperlipidaemia

[b] Patients with adverse events attributed to statin intolerance

Table 2 Summary of mono and combined lipid-modifying therapies (LMT), overall and for the familial hypercholesterolaemia (FH) subgroup

Treatment[a]	No. of patients (%)	
	Overall	FH
Monotherapy		
Statin	954 (76.7%)	234 (76.2%)
Other LMT	10 (0.8%)	1 (0.3%)
Ezetimibe	7 (0.6%)	2 (0.7%)
Combination therapy		
Statin + ezetimibe	132 (10.6%)	50 (16.3%)
Statin + other LMT	107 (8.6%)	11 (3.6%)
Statins + other LMT + ezetimibe	27 (2.2%)	9 (2.9%)
Other LMT + ezetimibe	7 (0.6%)	0 (0%)
Total	1244 (100%)	307 (100%)

[a] Anytime during the observation period. Each subject is included only once (e.g. if they received statin monotherapy for a portion of the observation period and statin + ezetimibe for another portion, they are included under statin + ezetimibe)

Patient characteristics are summarised in Table 1 and lifestyle risk factors in Table S2. Mean patient age was 63.3 (SD 11.3) years and the majority (63%) were men; duration of hyperlipidaemia ranged from < 1 year (17.7%) to ≥ 5 years (42.9%). Most (943; 75.8%) were secondary prevention patients, with almost 90% classified as VHR (1093; 87.9%). There were 307 patients (24.7%) with FH; 528 (42.4%) with diabetes and 208 (16.7%) with STEMI, with 127 (10.2%) being classified as statin intolerant (Table 1), as per "Methods" section.

Among those listed as having FH (n = 307), just over half had 'probable' or 'definite' FH (score ≥ 6; n = 170; 55.4%), according to Dutch Lipid Clinic Network (DLCN) criteria [12]. It is unclear whether FH was diagnosed clinically or genetically and whether the DLCN score was based on highest untreated LDL-C levels.

Table 3 Summary of statin use at the first visit of the observation period

Statin	Dose (mg)	Patients (%)
Atorvastatin	5–10	98 (7.9%)
	20–30	219 (17.7%)
	40–80	311 (25%)
Rosuvastatin	5	23 (1.9%)
	10–15	195 (15.7%)
	20–40	194 (15.6%)
Simvastatin	5–40	86 (6.9%)
Fluvastatin	40–80	8 (0.6%)
Pravastatin	10–40	8 (0.6%)
Lovastatin	10–40	3 (0.2%)
Unknown/not taking statins	–	99 (8.0%)
Total		1244 (100%)

Lipid-Modifying Therapies

As shown in Table 2, almost all patients received statins during observation: 954 (76.7%) as monotherapy and 266 (21.4%) as part of combination therapy. A total of 159 patients (12.8%) were taking a statin–ezetimibe combination, with/without other LMT. Statin dosage details were available for 1211 patients: 66/142 HR (46.5%) and 577/1069 VHR patients (54.0%) were taking high-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg/day) at some point during observation. Table 3 summarises statin type and dosages at first visit. Non-statin LMT is listed in Table S3: as well as ezetimibe ($n = 167$; 13.4%), this included fibric acid derivatives (117; 9.4%), proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i; 26; 2.1%), bile acid-binding resins (1; 0.1%) and niacin (1; 0.1%).

LDL-C Levels and Targets

Mean (SD) LDL-C levels tended to be lower at the latest visit than at the earliest visit of the retrospective period in all patient subgroups: 3.3 (1.7) ($n = 1244$) versus 2.7 (1.3) mmol/L ($n = 1205$) overall (Table S4; Fig. 1). Not unexpectedly, the FH subgroup had the highest mean (SD) LDL-C levels, at 5.1 (1.7) and 3.8 (1.5) mmol/L, respectively (Fig. 1). Patients with DLCN score 3-5 had slightly higher mean LDL-C than those with score $\geq$ 6. During the prospective period there was little change in mean LDL-C (Table S4). Comparison of mean LDL-C levels at the last visit showed the FH subgroup to have significantly higher, and the secondary prevention and diabetic subgroups to each have
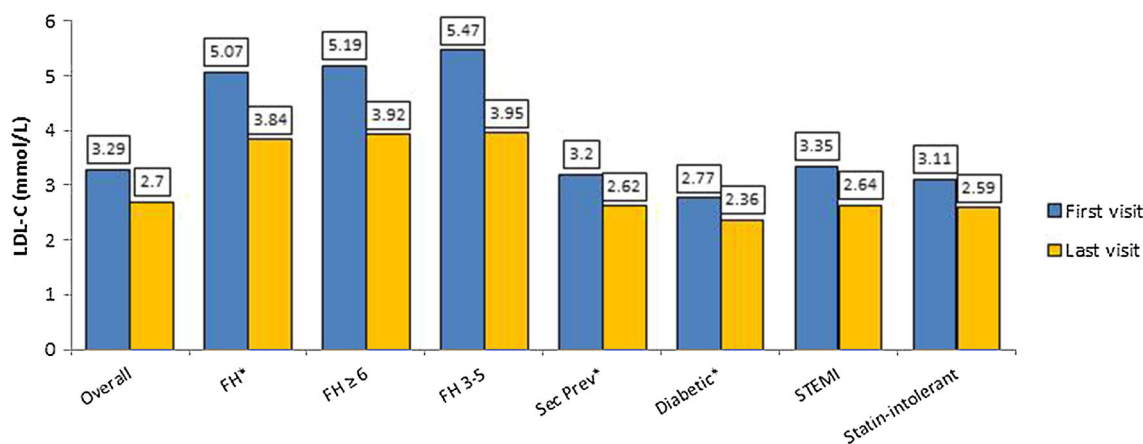
Fig. 1 Mean LDL-C levels, overall and by subgroup at the first and last visit of the retrospective period ($n = 1244$ first visit; 1204 last visit). FH, Familial hypercholesterolaemia; FH $\geq$ 6 and FH 3–5 refer to DLCN scores [12]; SI, patients with symptoms attributed to statin intolerance. For subgroup numbers, see Table S3. *$P < 0.001$ for last visit values versus rest of study population (Mann–Whitney U test)
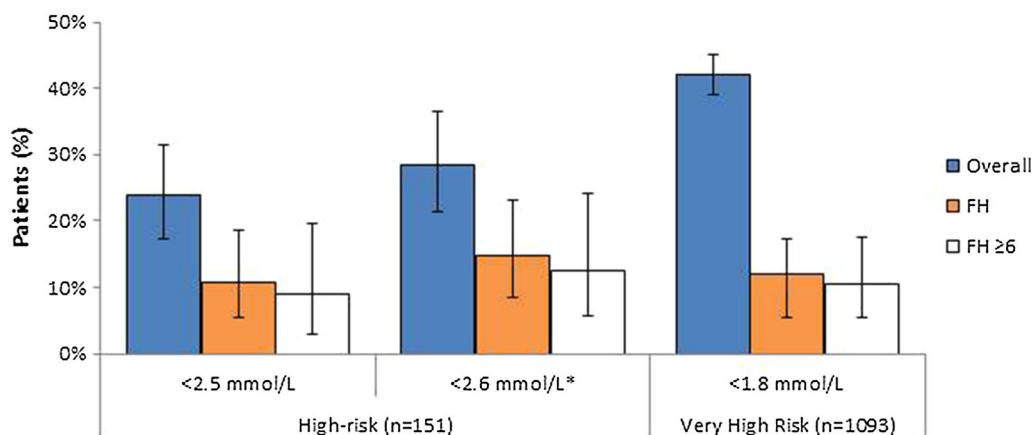
Fig. 2 Proportion of high-risk ($n = 151$) and very high risk ($n = 1093$) patients achieving ESC/EAS-defined LDL-C target at any time during the observation period; overall and for patients with FH (all FH patients and those with DLCN score ≥ 6). *Updated target in 2016 guidelines [8]

significantly lower, levels than the remainder of the study population ($p < 0.001$ all comparisons).

Achievement of risk-based ESC/EAS LDL-C targets (overall and FH patients) is shown in Fig. 2. In the HR group, 36/151 patients (23.8%; 95% CI 17.29–31.45%) achieved < 2.5 mmol/L and 43 (28.5%; 21.44–36.38%) achieved the current target of < 2.6 mmol/L, at some point during the observation period. Among the VHR patients, 459/1093 (42.0%; 39.05–44.98%) reached their target of < 1.8 mmol/L (Fig. 2). Post hoc analysis revealed that among the 577 VHR patients taking high-intensity statin treatment during the study, 261 (45.2%; 41.1–49.4%) patients reached their LDL-C goal versus 189 (38.4%; 34.1–42.9%) of those who did not receive high-intensity statins (Table S5). Approximately 60–70% of HR and 60% of VHR patients who did not reach their target were not taking high-intensity statins.

There was a higher rate of target achievement in the prospective versus the retrospective phase, consistent with the LDL-C levels seen in these periods (Table S6).

As summarised in Table S5, very few FH patients reached their LDL-C target: 10.9% (5.6–18.7%) of HR and 12.1% (8.0–17.4%) of VHR patients attained < 2.5 and < 1.8 mmol/L, respectively, with 14.9% of HR patients (8.6–23.3%) attaining < 2.6 mmol/L. In those

with definite/probable FH (DLCN score ≥ 6), 5/56 (8.9%; 3.0–19.6%) HR patients reached < 2.5 mmol/L and 7/56 (12.5%; 5.2–24.17%) achieved < 2.6 mmol/L, while 12/114 (10.5%; 5.6–17.7%) VHR patients achieved < 1.8 mmol/L. Similar results were seen in those with DLCN score 3–5.

Cardiovascular Events

As summarised in Table 4, 910 patients (73.2%) had a history of CV events ($n = 1$–6 events) at the start of observation and 523 patients (42.1%) experienced events ($n = 1$–8) during observation. In total 37/151 (24.5%) HR and 906/1093 (82.9%) VHR patients (total 943; 75.8%) experienced CV events prior to, or during, the observation period. (For a list of CV events that were captured in the study, see "Methods".)

Adverse Events and Hospitalisations

At enrolment, 127 patients (10.2%) were classified as statin intolerant; the most common symptom being statin-associated muscle symptoms (SAMS) as defined by an EAS Consensus Panel [13] (7.8% of patients overall). Other symptoms included hepatotoxicity, new-onset diabetes mellitus and other rare statin-associated adverse events ($< 1\%$ of patients overall).

Table 4 Summary of cardiovascular events

Number of events[a]	Patients (%)	
	Overall (*n* = 1244)	FH (*n* = 307)
Before start of observation (historical events)		
1	487 (39.1%)	109 (35.5%)
2	275 (22.1%)	41 (13.4%)
3	99 (8.0%)	18 (5.9%)
4	37 (3.0%)	6 (2.0%)
5	9 (0.7%)	1 (0.3%)
6	3 (0.2%)	0 (0%)
Total with events	910 (73.2%)	175 (57.0%)
During observation		
1	251 (20.2%)	75 (24.4%)
2	196 (15.8%)	77 (25.1%)
3	56 (4.5%)	18 (5.9%)
4	13 (1.0%)	4 (1.3%)
5	2 (0.2%)	0 (0.0%)
6	0 (0.0%)	0 (0.0%)
7	2 (0.2%)	0 (0.0%)
8	3 (0.2%)	0 (0.0%)
Total with events	523 (42.1%)	174 (56.7%)

[a] Coronary heart disease (unstable angina pectoris/myocardial infarction/sudden cardiac death), cerebrovascular disease (transient ischaemic attack/stroke) or peripheral artery disease (intermittent claudication/ischaemic rest pain/gangrene/abdominal aortic aneurysm/atrial fibrillation/heart failure/coronary revascularisation)

A total of 528 patients (42.4%) were hospitalised at least once during the observation period. Reasons included coronary revascularisation (*n* = 119; 9.6% of patients); heart failure (71; 5.7%); unstable angina pectoris (69; 5.6%), or STEMI, non-STEMI, atrial fibrillation, intermittent claudication, ischaemic pain at rest (1–5%).

Table 5 Most common reasons for switching/modifying/discontinuing lipid-modifying therapy (includes all reasons applying to > 5 patients in the overall group)

Status and reason[a]	*n* (%)	
	Overall	FH
Switched to other LMT (incl. statins)	163/1244 (13.6%)	25/307 (8.1%)
Insufficient lipid-lowering effect	83/163 (50.9%)	17/25 (68.0%)
Muscle pain and weakness	28/163 (17.2%)	4/25 (16.0%)
Financial reasons	6/163 (3.7%)	0/25 (0%)
Modified dose and/or frequency	214/1244 (17.8%)	59/307 (19.2%)
Insufficient lipid-lowering effect	141/214 (65.9%)	45/59 (76.3%)
Muscle pain and weakness	19/214 (8.9%)	6/59 (10.2%)
Financial reasons	6/214 (2.8%)	3/59 (5.1%)
Increased liver enzymes	6/214 (2.8%)	0/59 (0%)
Discontinued	65/1244 (5.4%)	22/307 (7.2%)
Muscle pain and weakness	19/65 (29.2%)	13/22 (59.1%)
Insufficient lipid-lowering effect	10/65 (15.4%)	3/22 (13.6%)

[a] Reasons are expressed as % of patients in each status

Changes in Lipid-Modifying Therapies

As summarised in Table 5, a total of 163 patients (13.6%) switched to other LMT, 214 (17.8%) had modifications in dose and/or frequency and 65 (5.4%) discontinued LMT. In the FH subgroup, 8.1% switched to other LMT, 19.2% had modifications in dose and/or frequency and 7.2% discontinued their LMT. The most common reasons for these changes were insufficient

lipid-lowering effect and muscle pain and weakness.

DISCUSSION

This observational study explored how elevated LDL-C in HR and VHR patients with dyslipidaemia is currently managed in central/eastern Europe and Israel. Our study population consisted mainly of VHR/secondary prevention patients attending specialist clinics; approximately 40% were diabetic and one-quarter had FH. Less than one-quarter (23.8%) of the HR patients and less than half (42.0%) of the VHR patients achieved their risk-based LDL-C targets of < 2.5 and < 1.8 mmol/L, respectively. The revised (2016) ESC/EAS target for HR patients (2.6 mmol/L) was met by 28.5% of our HR patients.

Our findings are consistent with numerous previous reports, from various geographical regions, of low rates of LDL-C target achievement in patients with hyperlipidaemia [14–17]. For instance, the EUROASPIRE IV survey of 6648 coronary heart disease (CHD) patients at 79 centres (largely academic hospitals) in 24 European countries found that at follow-up ≥ 6 months after hospital discharge, LDL-C values were < 2.5 mmol/L in 57.8% of patients and < 1.8 mmol/L in 19.3% of patients [14]. Similarly, the Dyslipidaemia International study (DYSIS), a survey of almost 58,000 statin-treated patients across Europe, the Middle East, Canada, Africa and Asia, found that only 21.7% of the VHR patients and 38.0% of the HR patients attained their LDL-C goals [15].

Fewer than 15% of our FH patients reached their LDL-C goals. Approximately half had probable or definite FH by DLCN criteria [1, 12] (score ≥ 6), which are based not only on LDL-C but also on family and clinical history and physical examination. FH diagnosis based on clinical criteria may lead to both false positive and false negative diagnoses when matched against genetic analysis, often reflecting polygenic, rather than monogenic, severe hypercholesterolaemia. For untreated patients with definite or probable FH, the risk of CHD is estimated to be ≥ 10-fold higher than the general population but can be substantially reduced with timely cascade screening and appropriate treatment. However, in practice it is an underdiagnosed and undertreated disease [18–20]. For instance, a Danish population survey in $> 69,000$ individuals found that only 48% of those with FH were receiving LMT. The adjusted odds ratio for coronary artery disease in those with definite/probable FH versus non-FH subjects was 13.2 (10.0–17.4) without LMT and 10.3 (7.8–13.8) with LMT [20].

Multiple issues may potentially contribute to inadequate LDL-C reduction in patients with hyperlipidaemia. Underdosing and statin discontinuation/poor adherence to therapy are acknowledged as key contributors and have been linked to poorer clinical outcomes [8, 13, 21]. Statin nonadherence is a challenge for clinicians and generally worsens over treatment duration, with many reports of adherence rates $< 50\%$, particularly in primary prevention settings [8, 21–23]. As discontinuation of statins and poor patient adherence to treatment can be related to SAMS, detailed expert guidelines for diagnosing and managing this condition have recently been published by an EAS Consensus Panel [13].

Financial/reimbursement issues may be an additional factor. Some countries have only partial reimbursement for drug treatment (e.g. Bulgaria with 25% reimbursement and 75% co-payment) which, together with low disposable income, can result in patients being restricted to cheaper treatments/lower doses. Ezetimibe is not reimbursed in some countries and this may have been a factor in the low usage of statin/ezetimibe combinations. Healthcare systems in the eastern Europe region are based on the reference pricing principle and therefore much more restrictive in permitting newer treatments, waiting for the largest markets to reimburse the new products and deliver data showing real-world results from the change in clinical practice.

Only half of our patients (53%) overall were taking high-intensity statin therapy and only 13% were receiving statin + ezetimibe combinations. Approximately 60–70% of HR and 60% of VHR patients who did not receive high-intensity statins did not achieve their target

during observation. Overall, 10% of patients were listed as having statin intolerance symptoms, most commonly SAMS (8% of patients). Despite most patients not reaching their LDL-C targets, only 14% switched to another LMT during the observation period, while 18% had modifications in dose and/or frequency, generally because of insufficient lipid-lowering or muscle pain/weakness. Only 5% of patients discontinued LMT. Financial reasons were cited as the reason for changing treatment in six patients (3.7%).

If LDL-C is extremely elevated, as is often the case in FH patients, even maximal-dosage statins plus ezetimibe may not be able to lower LDL-C to within the target range. Alternative treatments for hyperlipidaemia are urgently needed and are currently being developed.

Only 2% of our patients (mostly those in the SI group; $n = 22$) were receiving PCSK9is, which were only just becoming available in many of the participating countries at the time the study was being conducted. This class of drugs target the serine protease PCSK9, which plays a key role in LDL receptor (LDLR) activity [24]: inhibiting PCSK9 results in improved LDLR recycling and increased LDLR availability on hepatocyte cell surfaces. When added to existing maximally tolerated statin therapy, the monoclonal antibodies alirocumab and evolocumab can effect further LDL-C reductions of up to 60%, leading to target levels being met in up to 80% of patients [25–29]. Recently published outcome data from the FOURIER and ODYSSEY studies indicate that evolocumab (Repatha) [27] and alirocumab (Praluent) [30] significantly reduce the risk of CV events. Their safety profile differs substantially from that of statins, with no evidence of creatine kinase elevation, myalgia/muscle symptoms and few patients discontinuing treatment because of adverse events [26, 27, 29]. Further long-term safety data are awaited with interest. Recently updated guidelines from an ESC/EAS Task Force indicate that PCSK9i may be considered for VHR patients with atherosclerotic CVD (ASCVD), including those with progressive ASCVD or diabetes with target organ damage or a major CV risk factor or severe FH without ASCVD but severely elevated LDL-C despite maximal statin/ezetimibe therapy [31].

Almost half of our patients (42.1%) experienced one or more CV events during observation. This very high rate of events includes non-major events and reflects the nature of our study population, as well as the very high rate of CV events and mortality seen in many developing European countries [32].

Our observational study has some limitations. The study population was drawn mainly from cardiology, lipidology and diabetic clinics, and the mix of centres and patients differed between the participating countries, which limits the generalisability of our results. Patients had a variable duration of LMT, with approximately 20% being newly diagnosed. They were treated and monitored according to local clinical practice, with no prestipulated LDL-C measurement intervals. Lipid measurements were conducted at local laboratories; thus, there will be some differences due to assay biases between laboratories. As previously mentioned, the diagnosis of FH was uncertain for some patients. Nevertheless, our data provide a useful snapshot of hyperlipidaemia management patterns throughout the region. To our knowledge this is the first systematic study conducted in eastern Europe and Israel, other than EUROASPIRE [14].

CONCLUSIONS

Our findings provide real-world evidence from current clinical practice in eastern/central Europe and Israel. They confirm reports from other geographical areas that, despite widespread use of statins, many patients being treated for hyperlipidaemia, particularly those with FH, have persistent above-target LDL-C levels, thus remaining at risk of CV events. Further efforts are needed to address the unmet needs in these patients.

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Compliance with Ethics Guidelines. There were no study-related medical procedures undertaken. The study was conducted in accordance with the Helsinki Declaration of 1964, as revised in 2013, and with country-specific legal and regulatory requirements. It was approved by ethics committees and for registration or classification by regulatory bodies, as applicable in each country:

1. Bulgaria: Republic of Bulgaria Ministry of Health Ethics Committee for Multicentre Trial, Sofia; 2. Croatia: Agency for Medicinal Products and Medical Products Central Ethics Trust, Zagreb; 3. Czech Republic: Ethics Committee of: Faculty Hospital Hradec Králové, Králové; Institute for Clinical and Experimental Medicine (IKEM) and Thomayer Hospital, Prague; Faculty Hospital Brno, Brno; Faculty Hospital Plzeň, Plzeň; General Teaching Hospital in Prague, Prague; St. Anne's Faculty Hospital in Brno, Brno; Ethics Committee for Multicentre Clinical Assessment of the Motol University Hospital, Prague; Pardubice Regional Hospital Svitavska Hospital 4. Israel: Helsinki Committees of: Edith Wolfson Medical Centre, Tel Aviv; Chaim Sheba Medical Center, Tel Hashomer; Hadassah Medical Center, Jerusalem; Rabin Medical Center, Petah Tikva; Lady Davis Carmel Medical Center, Haifa; Soroka Medical Center, Beersheba; Bnai Zion Medical Center, Haifa; Meir Medical Center, Kfar Saba; Ziv Medical Center, Safed. 5. Poland: Bioethical Commission in Kielce at the Świętokrzyska Medical Chamber. 6. Romania: Romania Medical Sciences Academy, National Bioethics Committee for Medicines and Medical Devices, Bucharest. 7. Slovakia: Multicentre Ethics Committee of Kosice Self-Governing Region, Kosice.

The study followed generally accepted research practices described in Good Epidemiological Practice guidelines issued by the International Epidemiological Association. All data were handled in strictest confidence in conformity with national and European data protection regulations (such as Directive 95/46/EC). All patients provided written informed consent, where required by local regulations.

Data Availability. Data sharing requests relating to data in this manuscript will be considered after the publication date.

There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. A committee of internal advisors reviews requests.

Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available at the following: http://www.amgen.com/datasharing.

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