Advances in Therapy

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Clinical Management of High and very High Risk Patients with Hyperlipidaemia in Central and Eastern Europe: An Observational Study [1,2]

Petrov I., et al. Adv Ther. 2019

1. Petrov et al. 86th EAS, Lisbon, Portugal, May 05-08, 2019 (Abstract 359).
2. Petrov et al. *Adv Therapy* (Submitted manuscript).

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Abbreviations

- Cardiovascular (CV)
- European Society of Cardiology/European Atherosclerosis Society (ESC/EAS)
- High Risk (HR)
- Lipid-modifying treatment (LMT)
- Low density lipoprotein cholesterol (LDL-C)
- Protein convertase subtilisin/kexin type 9 inhibitors (PCSK9i)
- Very High Risk (VHR)

Background

- Hyperlipidaemia is a major modifiable risk factor for development of cardiovascular (CV) disease, the leading cause of death and disability in the developed world.[1]

- Reducing low density lipoprotein cholesterol (LDL-C), via lipid-modifying treatment (LMT), lowers the risk of CV events.[2-4]

- Every ~1 mmol/L reduction in LDL-C reduces the risk of major vascular events (coronary death/non-fatal myocardial infarction/coronary revascularization/stroke) by ~20%.[5]

1. World Health Organization. http://www.who.int/gho/publications/world_health_statistics/2017/en/.
2. Kannel WB. Washington, D.C., Dept. of Health, Education, and Welfare, Publication No. (NIH) 74-599, 1974.
3. Kannel WB. *Am J Cardiol.* **1995** 76, (9 Suppl 1): 69C-77C. 4. Kannel WB, et al. *Ann Intern Med* 1979; 90: 85-91.
5. Cholesterol Treatment Trialists C. *Lancet*; 376: 1670-1681.

Background (cont'd)

- 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 and this translates into a substantial burden of morbidity and mortality.[1]

- 2011 Guidelines from the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommended risk-based LDL-C targets for patients with hyperlipidaemia:
  - <2.5 mmol/L (96.5 mg/dL) for High Risk (HR) patients
  - <1.8 mmol/L (70 mg/dL) for Very High Risk (VHR) patients[2]
  - The target for HR patients was revised to <2.6 mmol/L (100mg/dL) in 2016[3]

1. Tolonen H, Keil U, Ferrario M, et al. Int J Epidemiol 2005; 34: 181-192.
2. Reiner Z, et al. *Eur Heart J* 2011; 32: 1769-1818.
3. Catapano et al. Atherosclerosis 2016; 253: 281-344.

Aim of Study

- We conducted a retrospective/prospective observational study (January 2015-February 2017) to gain insight into the current management of hyperlipidaemia in HR and VHR patients in central/eastern Europe and Israel.

- Many countries in this region have limited data available on LMT use and lipid control, due to lack of patient registries and access to public/health insurance data.

- We aimed to determine the proportion of HR and VHR hyperlipidaemia patients achieving ESC/EAS LDL-C targets and identify prevailing treatment patterns and CV event background.

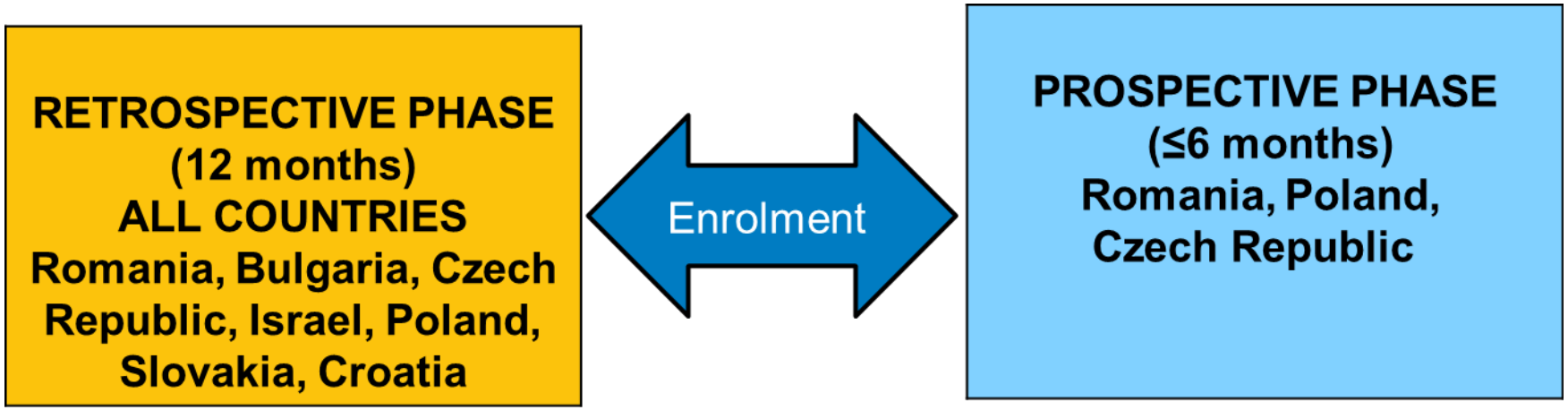
Inclusion Criteria

- Adult patients with hyperlipidaemia:
  - Receiving LMT and attending a specialist (cardiologist, diabetologist, lipidologist, internist) for a routine visit at participating sites.
  - ≥2 LDL-C values and valid LMT documentation (type of medication, dose) available for the retrospective phase and all LDL-C values and corresponding LMT information from the prospective phase.
  - Provided informed consent, according to local requirements, if participating in the prospective phase.
  - HR or VHR according to 2011 ESC/EAS Guidelines.[1]

1. Reiner Z, et al. Eur Heart J 2011; 32: 1769-18.

Study Schema

- Data were collected from patients' records, for the 12 months before enrolment, with up to 6 months' additional prospective follow-up in Romania, Poland and the Czech Republic.



Study Objectives

Primary study objective:

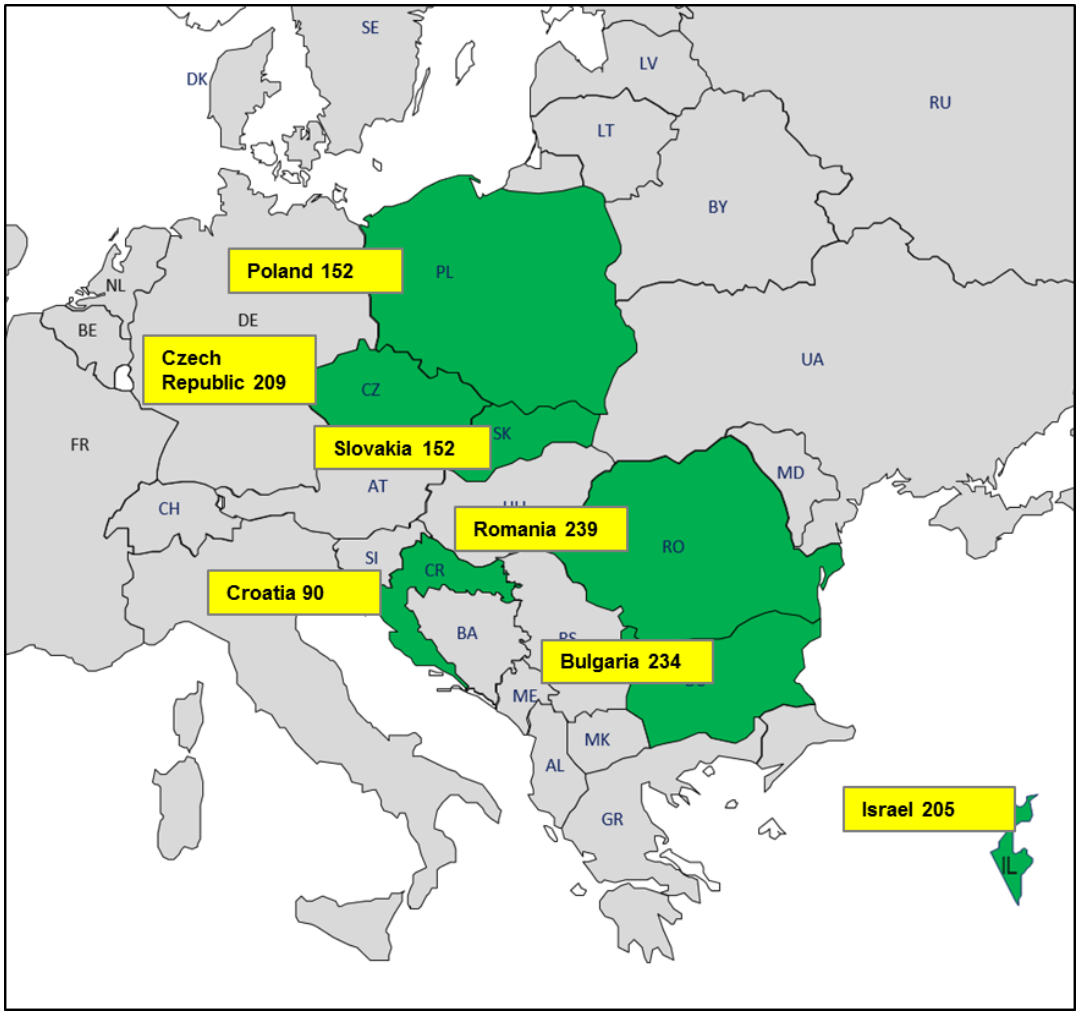
- proportion of patients achieving EAS-defined LDL-C target levels:
  - <2.5mmol/L (High-Risk)
  - <1.8 mmol/L (Very High Risk).[1]
- The updated target of <2.6 mmol/L for HR patients (ESC 2016 updated guidelines) was included in the analysis.[2]

Secondary objectives:

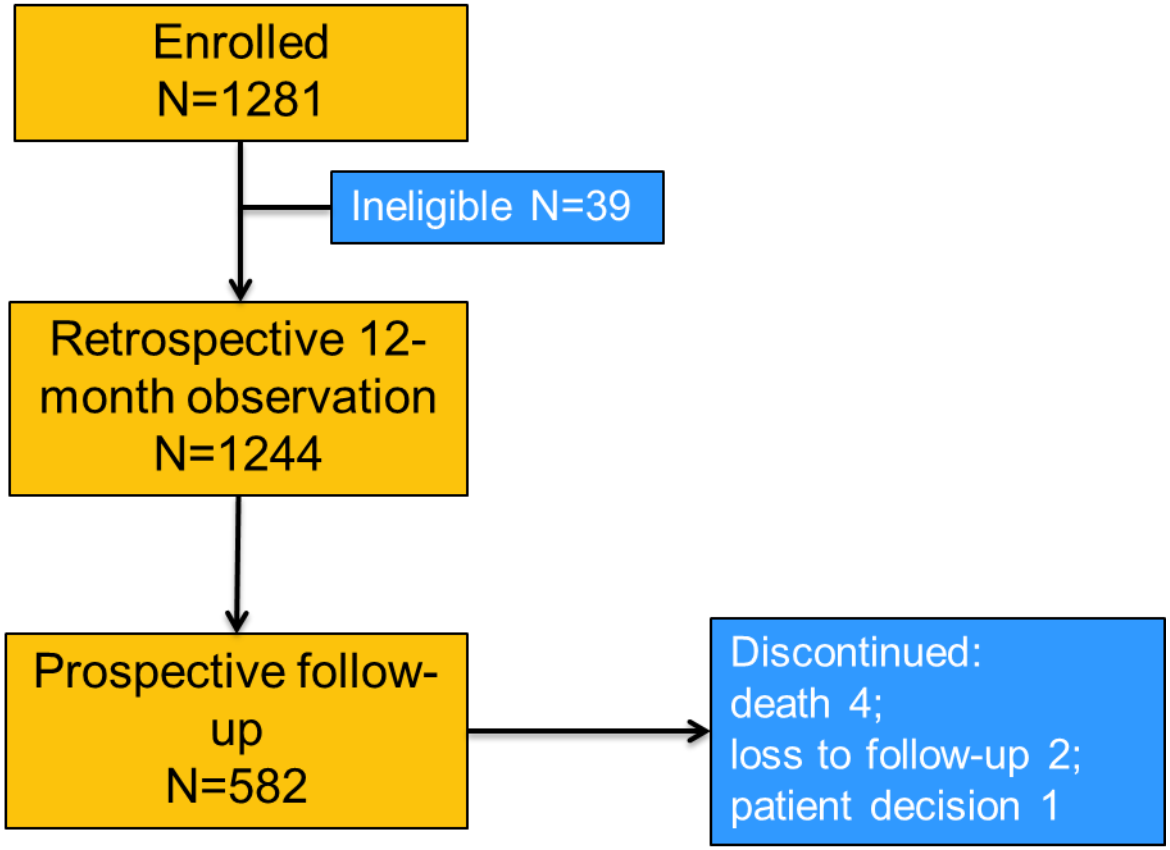
- LDL-C levels over time;
- use of statins and other LMT;
- patient characteristics;
- statin intolerance symptoms;
- CV events and hospitalizations.

1. Reiner Z, et al. Eur Heart J 2011; 32: 1769-18.
2. Catapano et al. Atherosclerosis 2016; 253: 281-344.

Patient Enrolment by Country



Patient Disposition

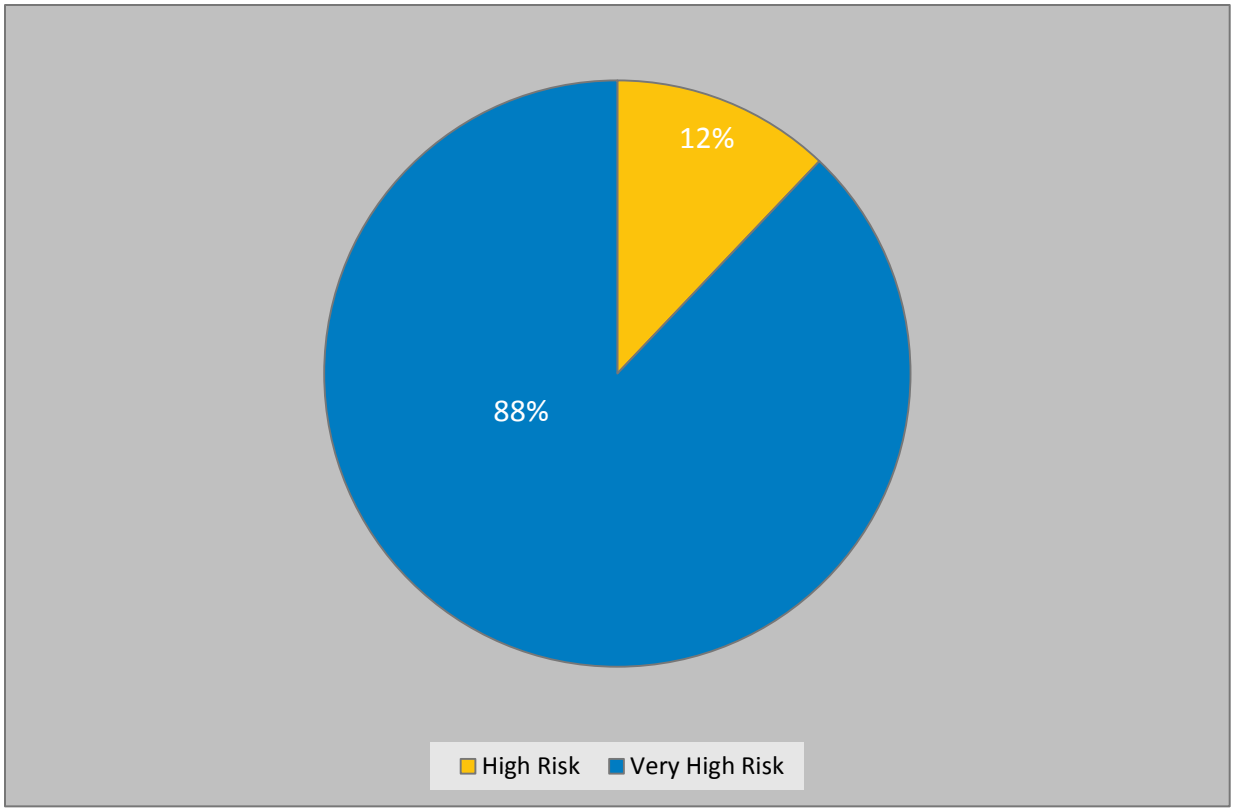


Study Population (n=1244)

Characteristic		
Male/Female	n/n	787/457
Age (Years)	Mean	63.3
	Range	18-92
Time since diagnosis*	<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%)

*Diagnosis of hyperlipidaemia.

Study Population (cont'd): Cardiovascular Risk Category1



1. Reiner Z, et al. Eur Heart J 2011; 32: 1769-18.

Study Population (cont'd)

		Patients (%)
Subgroup	Familial hypercholesterolaemia	307 (24.7%)
	Secondary prevention	943 (75.8%)
	Diabetes	528 (42.4%)
	STEMI	208 (16.7%)
	Hypertension	1023 (82.2%)
	Statin-intolerant*	127 (10.2%)
DLCN score (FH)	Unlikely (<3)	51 (16.3%)
	Possible (3 – 5)	86 (27.5%)
	Probable (6 – 7)	86 (27.5%)
	Definite (≥8)	84 (26.8%)

DLCN = Dutch Lipid Clinic Network criteria.

* Patients with adverse events attributed to statin intolerance.

Lipid-Modifying Therapies

Treatment	Patients (%)	
	Overall (n=1244)	**FH (n=307)**
Statin	954 (76.7%)	234 (76.2%)
Other LMT	10 (0.8%)	1 (0.3%)
Ezetimibe	7 (0.6%)	2 (0.7%)
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%)

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).

Summary of Statin Therapy at first visit

Statin	Dose (mg)	Patients (%)
Atorvastatin	5-10	98 (0.8%)
	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%)

A total of 643 patients (53.1%) - 66/142 HR (46.5%), and 577/1069 VHR patients (54.0%) - were receiving high-intensity statins (atorvastatin 40-80mg or rosuvastatin 20-40mg/day) during the study.

Non-Statin Treatments

Treatment	Patients (%)
Ezetimibe	167 (13.4%)
Fibric Acid Derivatives	117 (9.4%)
PCSK9i	26 (2.1%)
Niacin	1 (0.1%)
Colestipol	1 (0.1%)

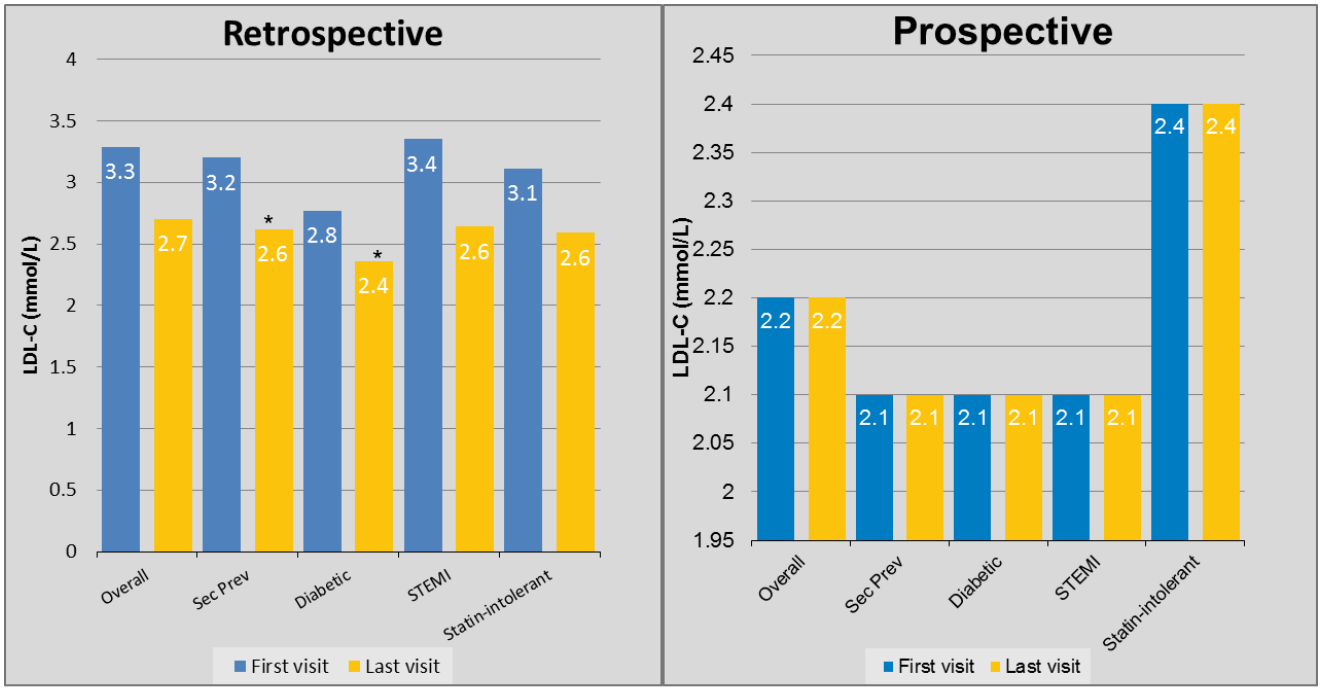
Changes in LMT

Status and Reason*	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
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
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%)

*Includes all reasons applying to >5 patients in the overall group). Reasons are expressed as % of status total.

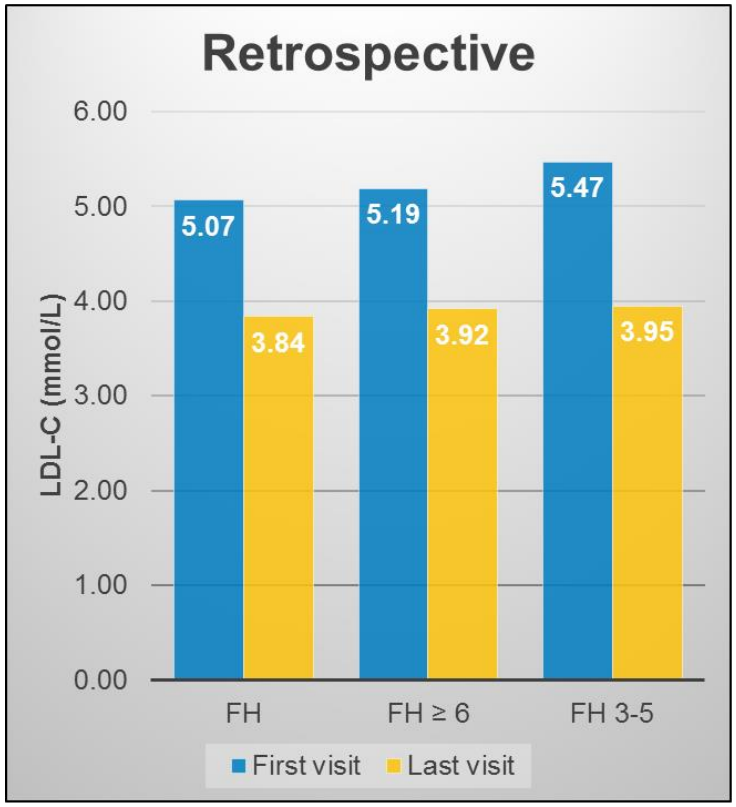
Mean LDL-C Levels by Subgroup

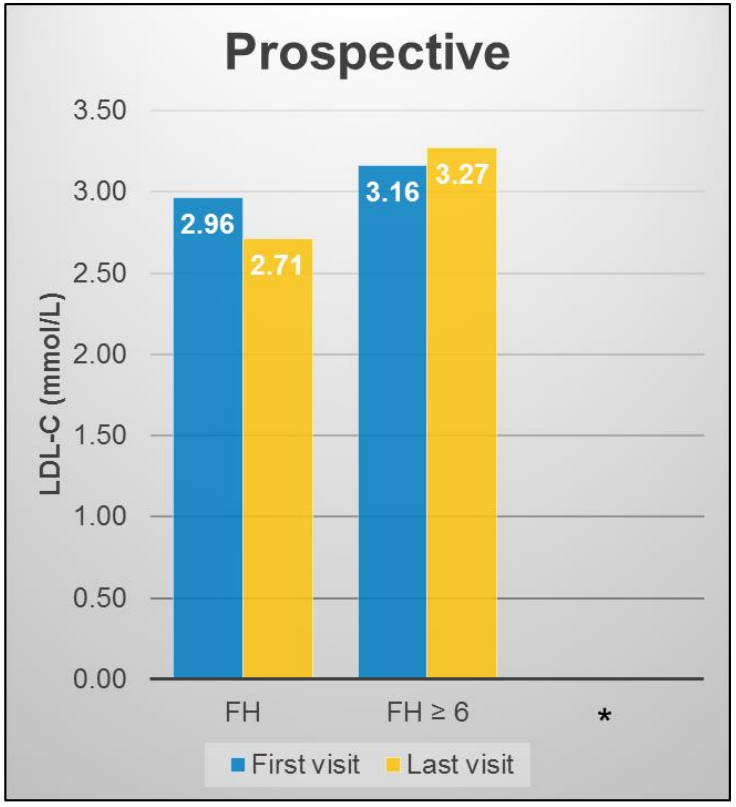
- Mean LDL-C was slightly lower at the last (n=1204) than the first (n=1244) visit of the retrospective phase but was similar for the first and second visits of the prospective period –NB number of patients decreased markedly (N=401 first visit; 165 last visit).



*P <0.001 *vs* remainder of patients at last visit. 'Statin-intolerant' refers to patients with adverse events attributed to statin intolerance.

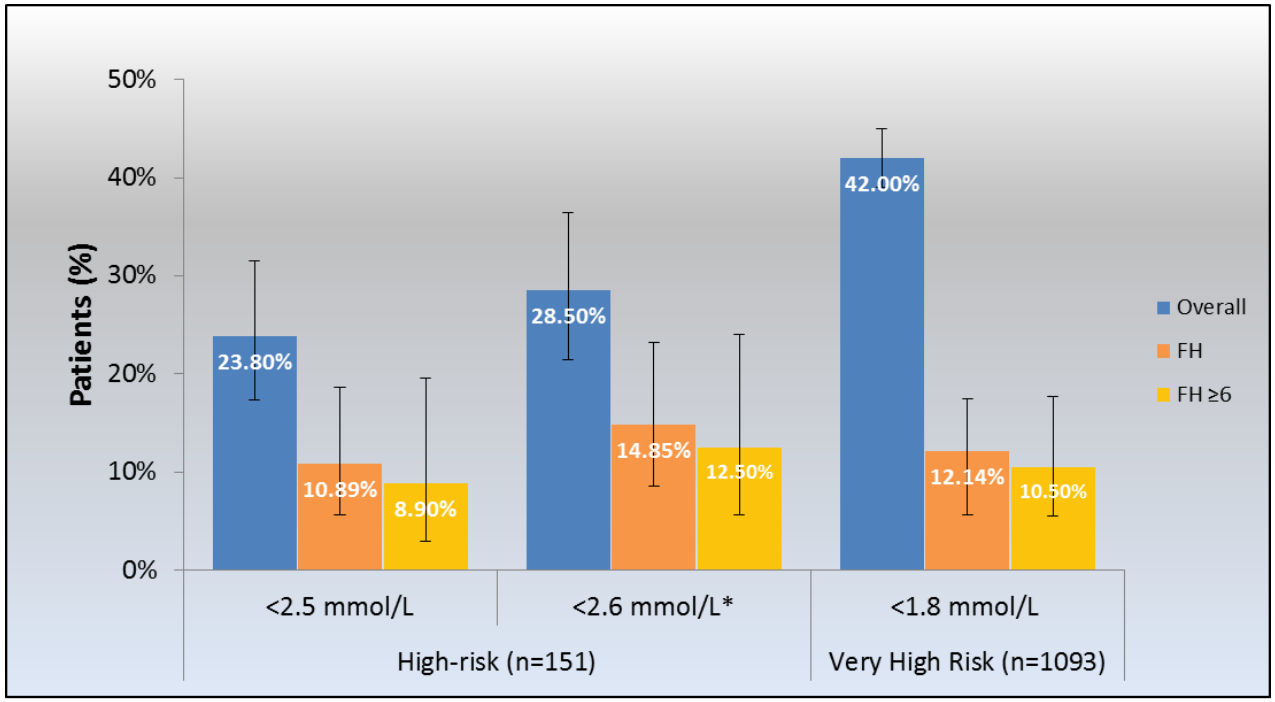
Mean LDL-C Levels FH subset (n=307)





*In the prospective phase there was only 1 patient with DLCN score 3-5, who did not have LDL-C data for the last visit.

ESC/EAS-defined LDL-C Target Achievement



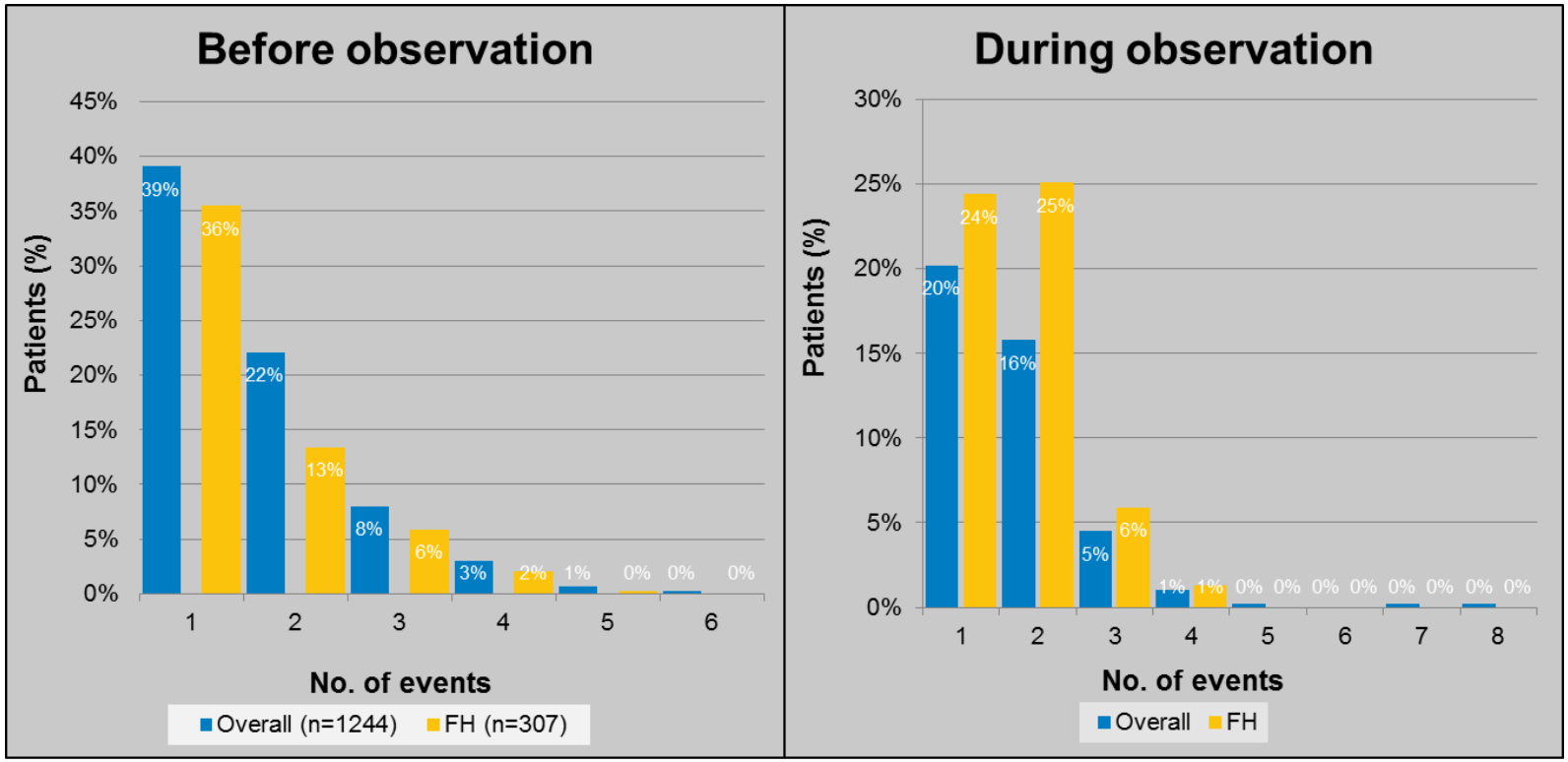
*Revised target in 2016 guidelines.[1]

FH = Familial hypercholesterolaemia; FH ≥6 indicates patients with Dutch Lipid Clinic Network criteria score ≥6.

1. Catapano et al. Atherosclerosis 2016; 253: 281-344.

Cardiovascular Events*

- CV events were recorded in 73.0% of patients overall (57.0% of FH subset) before observation, and in 42.1% (56.7% of FH subset) patients during observation.



*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).

Adverse Events

- Statin-Associated Muscle Symptoms were the most common adverse events associated with statin treatment:

Overall	FH	Secondary Prevention	Diabetic	STEMI	Statin Intolerant*
97/1244 (7.8%)	23/307 (7.5%)	74/943 (7.7%)	10/528 (4.8%)	37/208 (7.0%)	75/127 (59.1%)

- Other symptoms included hepatotoxicity, new-onset diabetes mellitus and other rare statin-associated adverse events (<1% of patients).

* Patients with adverse events attributed to statin intolerance.

Why don't patients reach their LDL-C goals? [1,2]

- Using low statin doses without sufficient uptitration.
- Statin discontinuation/poor adherence to therapy can be a result of Statin-Associated Muscle Symptoms - expert guidelines now available.[3]
- Other LMT such as ezetimibe and fibrates not added where indicated
- Financial/reimbursement issues may be a factor.
- Lifestyle risk factors not addressed?

- Extremely elevated baseline LDL-C (eg FH patients)
- Even high-intensity statin regimens (eg, 40–80 mg atorvastatin or 10–20 mg rosuvastatin daily) can only reduce LDL-C by 50%.
- Adding ezetimibe can reduce by a further 15-20%.[4]

- Need for new treatment approaches - are being developed e.g.
- protein convertase subtilisin/kexin type 9 inhibitors (PCSK9i)

1. Vohnout B, et al. Atherosclerosis 2017, 263:e233.2. Banach M, et al. Int J Cardiol, 225:184-196. 3. Stroes ES, et al. Eur Heart J 2015, 36(17):1012-1022. 4. Catapano et al. Atherosclerosis 2016; 253: 281-344

Conclusions

- Data from this multi-country observational study provide a useful 'Real-Life' snapshot of patient management patterns across the Central/Eastern European region and Israel.
- Approximately half of patients (53%) were taking high-intensity statins; only 13% were receiving statin + ezetimibe combinations.
- Only 24% of HR, and 42% of VHR patients achieved their risk-based LDL-C targets of <2.5 and <1.8 mmol/L, respectively, with even lower target attainment in the subset with definite/probable FH (9% and 11%, respectively).

Conclusions (cont'd)

- The 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, are undertreated and do not reach recommended LDL-C targets.

- Thus, these patients remain at excess cardiovascular risk, as evidenced by the high incidence of CV events during and before our study.

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Medical Writing and Other Assistance

- Julia Balfour of Northstar Medical Writing and Editing, Dundee, UK, drafted and revised the manuscript together with the authors, with financial support from Amgen. Joshua David and Mohamed Riaz Anwar of Quartesian, Bangalore, provided the statistical analysis.

Acknowledgments

Authorship

- All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions

- Ivo Petrov, Beata Wożakowska-Kapłon, Hrvoje Pintarić, Ian Bridges and Reneta Petkova contributed to conception and/or or design of the study. All authors contributed to acquisition, analysis, and/or interpretation of data for the work, critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Disclosures

- Ian Bridges is an employee and stockholder of Amgen. Reneta Petkova is an employee and stockholder of Amgen. Ivo Petrov has received research grants from Quintiles, consulting fees from Amgen, Actavis, Novartis, Medtronic, MSD, Boehringer Ingelheim, Pfizer and speaker honoraria from Amgen, Minvasys and Contego Medical. Michaela Snejdrlova discloses honoraria as a speaker for Amgen, MSD, Servier and Mylan and Research support from the Czech Ministry of Health. Lubomira Fabryova has received consulting fees from Abbott, Amgen, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, Sanofi Aventis, Servier, Valeant and speaker honoraria from Amgen, MSD, Sanofi Aventis and Valeant. Barak Zafrir has received consulting fees from Medison Israel and Sanofi Israel. Andreea Dumitrescu, Beata Wożakowska-Kapłon and Hrvoje Pintarić have nothing to disclose.

Acknowledgments

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.

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