ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2022) **8**, 447–460
https://doi.org/10.1093/ehjqcco/qcac009

ORIGINAL ARTICLE

Low-density lipoprotein cholesterol levels exceed the recommended European threshold for PCSK9i initiation: lessons from the HEYMANS study

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Received 26 November 2021; revised 4 February 2022; accepted 14 February 2022; online publish-ahead-of-print 17 February 2022

Aims To describe the characteristics of patients receiving evolocumab in clinical practice across 12 European countries and simulate the association between low-density lipoprotein cholesterol (LDL-C) reduction and cardiovascular (CV) risk reduction.

Methods and results The characteristics of hyperlipidaemic patients at initiation of evolocumab and treatment patterns study—HEYMANS ($n = 1952$) is a prospective registry of patients ≥18 years old who initiated evolocumab from 1 August 2015 onwards. Mean (standard deviation) age was 60 (10.8), 85% had a prior CV event, 45% were diagnosed with familial hypercholesterolaemia (FH), and 60% had statin intolerance. At evolocumab initiation, 43% were receiving any statin, 16% were receiving ezetimibe without statin, and 41% received no background lipid-lowering therapy (LLT), with LDL-C levels reflecting local proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) reimbursement criteria. Median LDL-C decreased from 3.98 to 1.63 mmol/L within 3 months of evolocumab initiation and was maintained over 24 months. Overall, 58% achieved risk-based 2019 European Society of Cardiology/European Atherosclerosis Society LDL-C goals but that proportion was higher (68%) in patients receiving background LLT compared with those not receiving background LLT (44%). In patients with atherosclerotic cardiovascular disease without FH, the simulated relative CV risk reduction associated with evolocumab treatment was 34% (25–44%).

Conclusion Across Europe, LDL-C levels at evolocumab initiation were three times higher than recommended thresholds for PCSK9i initiation, reflecting disparities between implementation and guidelines. More patients attained risk-based LDL-C goals when receiving evolocumab in combination with LLT vs. those not receiving combination therapy. Population health could be improved and LDL-C goals better attained if LDL-C thresholds for PCSK9i reimbursement were lowered, enabling more patients to receive combination therapy when needed.

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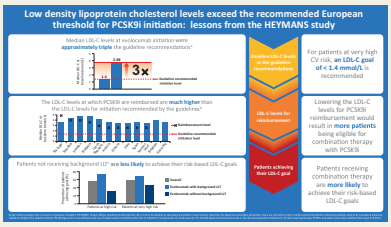
Graphical Abstract In a large registry study across Europe, low-density lipoprotein cholesterol levels at evolocumab initiation were three times higher than recommended thresholds for proprotein convertase subtilisin/kexin type 9 inhibitor initiation, reflecting disparities between reimbursement criteria and guidelines.



Keywords Evolocumab • PCSK9i • LDL-C • Registry • Guidelines • Cardiovascular risk

Introduction

Cardiovascular disease (CVD) remains the leading cause of death and disability in the world, contributing to more than 30% of the total global burden of disease.[1,2] Controlling lipid levels, in particular low-density lipoprotein cholesterol (LDL-C), is a proven therapeutic approach to reducing cardiovascular (CV) risk.[3] The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) 2019 guidelines recommend the use of a risk-based approach, advocating that those at greatest CV risk should aim to attain the lowest LDL-C levels.[4] Greater use of combination lipid-lowering therapies (LLTs) may be required to achieve the lower LDL-C goals recommended by the guidelines. The guidelines initially recommend a 50% lowering in LDL-C level from baseline and the use of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) for patients at very high CV risk when LDL-C goals of <1.4 mmol/L (<55 mg/dL) are not met despite patients receiving maximally tolerated statins and ezetimibe therapy.[4] For patients experiencing a second CV event within 2 years while receiving maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[4] These guidelines largely reflect the outcomes of large clinical trials and meta-analysis, which have consistently demonstrated that PCSK9is reduce LDL-C levels by at least an additional 50% when added to statin therapy or no background therapy and that lowering LDL-C levels reduces CV risk.[5–7]

In clinical practice, however, the LDL-C thresholds at which PCSK9is are reimbursed may be much higher than the LDL-C thresholds for initiation recommended by the guidelines.[4] The impact of this on guideline-recommended LDL-C goal attainment and residual CV risk has not been clearly characterized. Limited systematic data exist on how PCSK9is are used in routine clinical practice. A recent registry assessing the safety and efficacy of alirocumab in 944 patients at high CV risk from 16 European countries and Canada demonstrated that the addition of alirocumab to maximally tolerated LLT led to substantial reductions of LDL-C levels, which were sustained for over the duration of treatment and over half of the patients achieved the 2016 ESC/EAS LDL-C goals.[8] Yet, use of PCSK9is remains suboptimal in patients at very high CV risk. In the recent DA VINCI study, which included patients enrolled before publication of the 2019 ESC/EAS guidelines, ~80% of primary or secondary prevention patients treated with LLT were receiving either moderate- or high-intensity statin monotherapy regimens in Europe.[9] However, only 10% of patients receiving LLT were treated with combination therapy: 9% with both statins and ezetimibe and 1% received PCSK9is with an oral LLT.[9]

A better understanding of the characteristics of patients receiving PCSK9is in Europe could offer the medical community an opportunity to redefine existing care pathways to better implement evidence-based European guidelines, thus potentially reducing modifiable residual CV risk further. We sought to address gaps in our knowledge by conducting the characteristics of hyperlipidaemic patients at initiation of evolocumab and treatment patterns (HEYMANS) study (NCT02770131), which, to date, is the largest multicountry systematic registry of European PCSK9i use. Here, we describe the clinical characteristics and treatment patterns of those receiving evolocumab and assess the effect of this treatment on LDL-C reduction and goal attainment and simulate the potential CV risk reduction.

Methods

Study population and design

HEYMANS is a multicountry, multicentre, observational registry of European patients initiating evolocumab as part of their routine clinical management, based on local reimbursement criteria (*Table 1*). The planned sample size for the study was 2000 patients across 15 countries: Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Italy, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, and the UK. Of the 2000 planned patients, 1952 were enrolled from 12 countries. France, Poland, and the UK were excluded from the study owing to logistical limitations and expected low recruitment rates. Patients were included in the study if they were 18 years or older; with a first prescription of evolocumab after 1 August 2015; received at least one dose of evolocumab; and provided informed consent (if applicable according to local requirements). Patients who were enrolled in an interventional study of PCSK9i within 12 weeks prior to initiation of evolocumab or patients who received a PCSK9i within 12 weeks prior to initiation of evolocumab were excluded from the study. The baseline period of the study was defined as the period 6 months before the first dose of evolocumab through to the date of administration of the first dose of evolocumab. Patients were followed up for 30 months after evolocumab initiation, death, withdrawal of consent, or loss to follow-up, whichever occurred first. The first patient initiated evolocumab therapy on 4 May 2016 and the present interim report includes baseline and follow-up data collected up to 31 July 2020.

Table 1 Reimbursement criteria for evolocumab per country included in HEYMANS

Country	Reimbursement in primary prevention patients (FH)	Reimbursement in secondary prevention patients (established ASCVD)
Austria	• FH	• LDL-C > 100 mg/dL (2.6 mmol/L) • Statin-intolerant patients with LDL-C > 100 mg/dL (2.6 mmol/L)
Belgium	• HeFH: DLCN score > 8 and LDL-C ≥ 130 mg/dL (3.4 mmol/L) after treatment with statins and ezetimibe, or treatment with ezetimibe only if statin intolerant • HoFH: LDL-C ≥ 130 mg/dL (3.4 mmol/L) after treatment with statins and ezetimibe, or treatment with ezetimibe only if statin intolerant	• HeFH: DLCN score > 8 and LDL-C ≥ 100 mg/dL (2.6 mmol/L) after treatment with statins and ezetimibe, or ezetimibe only if statin intolerant • HoFH: LDL-C ≥ 100 mg/dL (2.6 mmol/L) after treatment with statins and ezetimibe, or ezetimibe only if statin intolerant
Bulgaria	• HeFH: DLCN score ≥ 6 and LDL-C > 5 mmol/L after treatment with statins for 6 months	• HeFH: DLCN score ≥ 6 AND • LDL-C > 3.6 mmol/L after treatment with statins for 6 months for patients with one CV event OR • LDL-C > 2.6 mmol/L after treatment with statins for 6 months for patients with more than one CV event
Czech Republic	• FH: LDL-C > 150 mg/dL (3.1 mmol/L)	• LDL-C > 115 mg/dL (2.6 mmol/L)
France[a]	• HoFH • HeFH and HoFH: patients needing LDL apheresis	• LDL-C > 70 mg/dL (1.8 mmol/L) after maximally tolerated doses of statins
Germany	• HoFH patients receiving dietary therapy and max. LLT • Confirmed HeFH patients with respect to the overall familial risk, if the following conditions are met: ○ Therapy refractory course of disease defined by insufficient LDL-C lowering ○ Max. tolerable LLT documented over 12 months ○ Indication for lipid apheresis	• HoFH patients receiving dietary therapy and max. LLT • HeFH, non-FH, or mixed dyslipidaemia patients with confirmed vascular disease and additional risk factors, if the following conditions are met: ○ Therapy refractory course of disease defined by insufficient LDL-C lowering ○ Max. tolerable LLT documented over 12 months ○ Indication for lipid apheresis
Greece	• HeFH • HoFH	• After MI or CABG, coronary angioplasty bypass, IS: LDL-C > 100 mg/dL (2.6 mmol/L) after maximally tolerated doses of statins and ezetimibe
Italy	• HoFH: aged ≤ 80 years • HeFH: LDL-C ≥ 130 mg/dL (3.4 mmol/L) after at least 6 months of treatment with high-intensity statins and ezetimibe or patients with statin intolerance	• LDL-C ≥ 100 mg/dL (2.6 mmol/L) after at least 6 months of treatment with high-intensity statins and ezetimibe or patients with statin intolerance • Patients ≤ 80 years with familial or non-FH or with mixed dyslipidaemia
Poland[a]	• FH: LDL-C > 160 mg/dL (4.1 mmol/L)	• Age ≥ 18 years AND • Two MIs, including one MI within the past year + MVCAD (defined by the presence of ≥50% diameter stenosis of two or more epicardial coronary arteries) OR • MI within past year + IS OR • MI within past year + PAD, defined as: intermittent claudication with ankle-brachial index <0.85; peripheral artery revascularization; or limb amputation due to atherosclerotic disease OR

Table 1 Continued

Country	Reimbursement in primary prevention patients (FH)	Reimbursement in secondary prevention patients (established ASCVD)
		• MI within last year + TIA AND • LDL-C level > 100 mg/dL (2.6 mmol/L) despite diet and intensive statin treatment in maximally tolerated doses, and then with ezetimibe, used for 3 months, including minimum 1 month of combined treatment.
Portugal	• FH: LDL-C > 130 mg/dL (3.4 mmol/L)	• LDL-C > 190 mg/dL (4.9 mmol/L) • DM: LDL-C > 160 mg/dL (4.1 mmol/L)
Slovakia	• HeFH: LDL-C > 5 mmol/L after 6 months of treatment with statins plus 1 month of treatment with ezetimibe, or 1 month of treatment with ezetimibe only if statin intolerant	• After 6 months of treatment with statins plus 1 month of treatment with ezetimibe, or 1 month of treatment with ezetimibe only if statin intolerant ○ LDL-C > 4 mmol/L in patients with one CV event ○ LDL-C > 3.5 mmol/L in patients with more than one CV event • HeFH: LDL-C > 3.5 mmol/L
Spain	• HoFH: patients not controlled on maximally tolerated doses of statins or statin intolerant, with LDL-C > 100 mg/dL (2.6 mmol/L) • HeFH: patients not controlled on maximally tolerated doses of statins or statin intolerant, with LDL-C > 100 mg/dL (2.6 mmol/L)	• Patients not controlled on maximally tolerated doses of statins or statin intolerant, with LDL-C > 100 mg/dL (2.6 mmol/L)
Sweden	• Updated in 2019—FH: LDL-C > 3.0 mmol/L despite treatment with statins and ezetimibe	• Initially: FH and post-MI only, with LDL-C > 155 mg/dL (4 mmol/L) • Updated in 2019—LDL-C > 2.5 mmol/L for patients not controlled on maximally tolerated doses of statins and ezetimibe
Switzerland	• HeFH: LDL-C > 5 mmol/L, with additional risk factors • HoFH: LDL-C > 5 mmol/L • Updated in 2019—After maximally tolerated doses of statins and ezetimibe, or treatment with ezetimibe only if statin intolerant: ○ HeFH: LDL-C > 5 mmol/L (LDL-C 4.5 mmol/L, with additional risk factors) ○ HoFH: LDL-C > 5 mmol/L	• LDL-C > 3.5 mmol/L (or 2.6 mmol/L for rapid progression) • Updated in 2019–After maximally tolerated doses of statins and ezetimibe, or treatment with ezetimibe only if statin intolerant: LDL-C > 2.6 mmol/L
UK[a]	• HeFH: LDL-C persistently ≥5.0 mmol/L • HoFH (only in Wales)	• Primary non-FH or mixed dyslipidaemia ○ with at least one CV event: LDL-C persistently ≥4.0 mmol/L ○ with recurrent CV events/polyvascular disease: LDL-C persistently ≥3.5 mmol/L • HeFH with CVD: LDL-C persistently ≥3.5 mmol/L

ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CVD, cardiovascular disease; DLCN, Dutch Lipid Clinic Network; DM, diabetes mellitus; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; MI, myocardial infarction; MVCAD, multivessel coronary artery disease; PAD, peripheral artery disease; and TIA, transient ischaemic attack.

[a]France, Poland, and the UK were excluded from the study owing to logistical limitations and expected low recruitment rates.

Outcomes

For this study, results are presented for the overall population and further stratified by clinically relevant subgroups: 'atherosclerotic cardiovascular disease (ASCVD) without familial hypercholesterolaemia (FH)'; 'ASCVD with FH'; 'FH without ASCVD'; and 'neither FH nor ASCVD'. Clinical characteristics of patients at initiation of evolocumab included demographics (e.g. age, gender, and country), CV risk factors (e.g. body mass index, hypertension, chronic kidney disease, smoking status, and vascular bed involvement), laboratory values (e.g. LDL-C, lipid parameters, and haemoglobin A1C), comorbidities (e.g. hypertension and diabetes), and other LLTs (e.g. statins and ezetimibe). The characterization of comorbidities was defined by national criteria among sites that primarily follow the ESC/EAS guidelines.[10] Statin intolerance was determined primarily through patient-reported symptoms, at the discretion of the investigator. LDL-C measurements were collected as per clinical practice, and changes in LLT were recorded. LDL-C levels were summarized during each 3-month window and evolocumab and LLT use at the end of each 3-month period was summarized. The proportion of

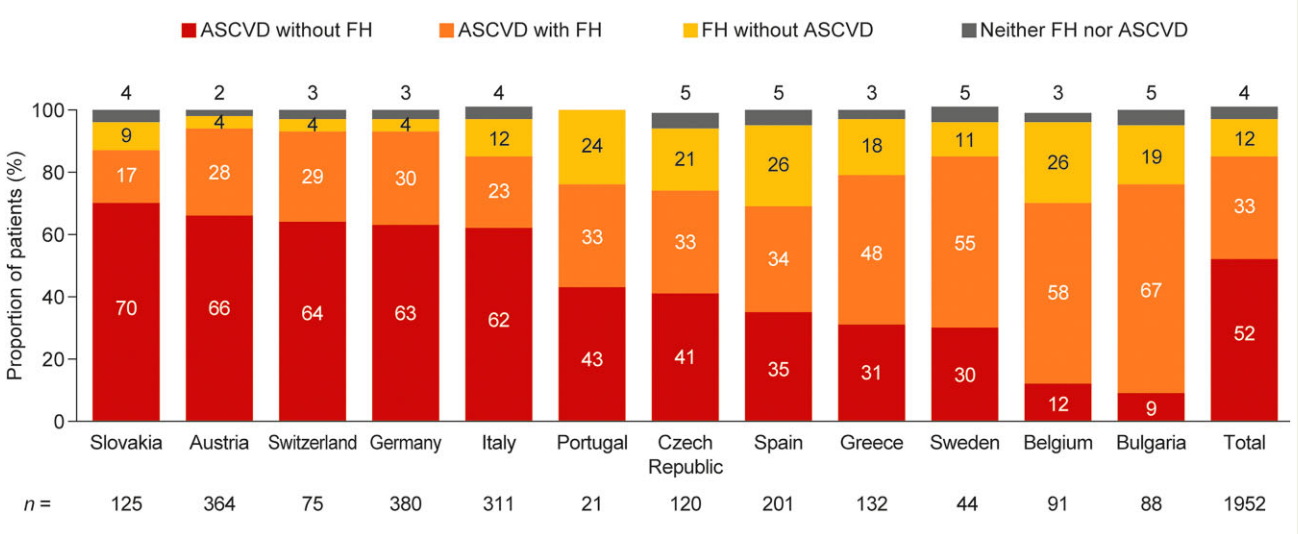


Figure 1 Proportion of patients in each subgroup by country. Data do not sum to 100% due to rounding. ASCVD, atherosclerotic cardiovascular disease; and FH, familial hypercholesterolaemia.

patients achieving their risk-based LDL-C goal at least once during the entire follow-up, determined according to the 2019 ESC/EAS guidelines, was calculated. All patients with ASCVD were categorized as very high risk (with an LDL-C goal of <1.4 mmol/L) and patients with FH were categorized as either high risk (with an LDL-C goal of <1.8 mmol/L) or very high risk (with an LDL-C goal of <1.4 mmol/L), in the presence of ASCVD or other significant risk factors. No formal analysis of safety data was planned for this study. Adverse drug reactions (ADRs) were categorized as treatment emergent, serious, fatal, or device related. All fatal adverse events were recorded.

For patients in the 'ASCVD without FH' group, the 10-year CV risk before evolocumab treatment was predicted or simulated using three different methods (and adjusting by age and baseline LDL-C): (1) prediction using the REduction of Atherothrombosis for Continued Health (REACH) equation[11] (the 20-month risk estimated from the equation was converted to a 10-year risk assuming an exponential survival function); (2) Monte Carlo simulation (assuming a beta distribution) based on the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk (FOURIER) trial (placebo arm) risk;[12] and (3) Monte Carlo simulation (assuming a beta distribution) based on FOURIER-like observational data (standard of care) risk.[13] For patients in the 'FH without ASCVD' group, the predicted 10-year CV risk before evolocumab was estimated using the Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART) algorithm.[14]

The potential CV risk reduction after evolocumab treatment was only simulated in the 'ASCVD without FH' group, given the potential challenges and underestimation of baseline risk in the 'FH without ASCVD' group using the SAFEHEART algorithm.[15,16] First, the absolute LDL-C reduction on evolocumab (in mmol/L) was calculated for each patient and assumed to be constant over time. Second, the relative risk reduction (RRR) was calculated by performing Monte Carlo simulation (assuming a log-normal distribution) on the rate ratio per 1 mmol/L from the FOURIER clinical trial key secondary endpoint landmark analysis.[5] Finally, the 10-year absolute risk reduction (ARR) and number needed to treat (NNT) were calculated. All simulations were performed using Microsoft Excel 2021.

Statistical analysis

Data are presented descriptively, using summary statistics, displaying frequency, percentage and 95% confidence interval (CI, where appropriate) for categorical data, and mean with standard deviation or median [interquartile range (Q1–Q3)] for continuous data.

Summaries are based on observed data, with no imputation applied for patients who did not have data at specific time points.

For assessment of LDL-C goal attainment, patients were included in the analysis if they had at least one post-baseline LDL-C value and were classified as high or very high risk according to the ESC/EAS guideline.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethical conduct of the study

The study was performed in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with the International Council for Harmonisation. The study was reviewed by an independent ethics committee in each country. Written informed consent was provided by all patients.

Results

Patient characteristics

In total, 1952 patients from 12 countries were included, with the majority enrolled in Germany ($n = 380$), Austria ($n = 364$), Italy ($n = 311$), and Spain ($n = 201$), as shown in the Supplementary material online, *Figure S1*. Of the 1952 patients enrolled, 1009 (52%) were categorized as 'ASCVD without FH', 642 (33%) were categorized as 'ASCVD with FH', 232 (12%) were categorized as 'FH without ASCVD', and 69 (4%) were categorized as 'neither FH nor ASCVD' (*Figure 1*). In the overall population, the mean (standard deviation) age was 60 years (11); 37% of patients were aged 65 years or older, and the majority were male (62%) (*Table 2*). Most patients (85%) had experienced a prior CV event, 65% had hypertension,

Table 2 Baseline characteristics and cardiovascular risk factors

	Overall (*N* = 1952)	ASCVD without FH (*n* = 1009)	ASCVD with FH (*n* = 642)	FH without ASCVD (*n* = 232)	Neither FH nor ASCVD (*n* = 69)
Female	733 (38)	309 (31)	243 (38)	138 (60)	43 (62)
Age (years), mean (SD)	60 (11)	63 (10)	59 (10)	52 (13)	59 (10)
LDL-C (mmol/L), median (Q1–Q3)	3.98 (3.17–5.07)	3.68 (2.97–4.60)	4.00 (3.24–5.09)	5.22 (4.11–6.48)	5.17 (4.11–6.20)
Non-HDL-C (mmol/L), median (Q1–Q3)	4.58 (3.70–5.82)	4.22 (3.52–5.40)	4.40 (3.75–5.52)	5.49 (4.63–7.53)	3.79 (3.05–5.00)
Hypertension	1271 (65)	742 (74)	427 (67)	56 (24)	46 (67)
Current smoker	275 (14)	133 (13)	92 (14)	37 (16)	13 (19)
Body mass index					
<20	53 (3)	25 (3)	18 (3)	8 (3)	2 (3)
≥20 and <30	1380 (71)	690 (68)	463 (72)	183 (79)	44 (64)
≥30	486 (25)	273 (27)	153 (24)	39 (17)	21 (30)
Type 2 diabetes mellitus	376 (19)	235 (23)	100 (16)	18 (8)	23 (33)
Chronic kidney disease	137 (7)	85 (8)	46 (7)	2 (1)	4 (6)
Statin intolerance	1176 (60)	681 (68)	310 (48)	131 (57)	54 (78)
FH diagnosed	874 (45)	0 (0)	642 (100)	232 (100)	0 (0)
High risk	91 (11)	0 (0)	0 (0)	91 (41)	0 (0)
Very high risk	783 (89)	1009 (100)	642 (100)	141 (59)	0 (0)
Prior CV event	1660 (85)	1009 (100)	642 (100)	5 (2)	4 (6)
Previous ACS[a]	828 (42)	553 (55)	275 (43)	0 (0)	0 (0)
CAD or angina[b]	1139 (58)	736(73)	403 (63)	0 (0)	0 (0)
PAD	229 (12)	154 (15)	75 (12)	0 (0)	0 (0)
Ischaemic stroke	122 (6)	84 (8)	38 (6)	0 (0)	0 (0)
Critical limb ischaemia	24 (1)	18 (2)	6 (1)	0 (0)	0 (0)
Carotid artery disease	438 (22)	245 (24)	193 (30)	0 (0)	0 (0)
TIA	52 (3)	39 (4)	13 (2)	0 (0)	0 (0)
Coronary thrombosis[c]	328 (17)	203 (20)	125 (14)	0 (0)	0 (0)

Data are all *n* (%) unless otherwise specified.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; SD, standard deviation; STEMI, ST-elevation myocardial infarction; and TIA, transient ischaemic attack.
[a]'Previous ACS' is a history of acute coronary syndrome, ST-elevation myocardial infarction, or non-ST-segment-elevation myocardial infarction.
[b]'CAD or angina' is a history of coronary artery disease or stable angina.
[c]Coronary thrombosis (acute or non-acute) is counted as one prior cardiovascular event.

51% were current or former smokers, and 60% were statin intolerant (*Table 2* and Supplementary material online, *Table S1*). Overall, 45% (*n* = 874) of patients had a diagnosis of FH (*Table 2 and* Supplementary material online, *Table S2*).

Patients in the 'FH without ASCVD' subgroup were more likely to be female than patients in the 'ASCVD without FH' and 'ASCVD with FH' subgroups (60% vs. 31% and 38%, respectively). Patients in the 'FH without ASCVD' subgroup were also likely to be younger than patients in the 'ASCVD without FH' and 'ASCVD with FH' subgroups, with a higher baseline median LDL-C (*Table 2* and Supplementary material online, *Table S1*).

Evolocumab and other lipid-lowering therapy use at baseline and during follow-up

LLT use before and after evolocumab initiation is depicted in *Figure 2*.

In general, LLT use remained stable; use of any statin without ezetimibe ranged from 12% to 14% and use of ezetimibe without a statin ranged from 13% to 17% across countries. At evolocumab initiation, approximately one-third of patients (31%) were receiving a statin with ezetimibe and 16% were on ezetimibe alone. Overall, 41% were not receiving any background therapy, primarily owing to statin intolerance which was investigator reported, and this varied according to subgroup and country. The proportion of patients not receiving background therapy in the 'ASCVD without FH', 'ASCVD with FH', and 'FH without ASCVD' groups was 46%, 33%, and 32%, respectively. Belgium had the lowest proportion of patients without background LLT at initiation of evolocumab in all three subgroups: 27% in the 'ASCVD without FH' group; 6% in the 'ASCVD with FH' group; and 8% in the 'FH without ASCVD' group. In the 'ASCVD without FH' group, Sweden had the highest proportion of patients without background LLT (85%), whereas in the 'ASCVD with FH' group, Czech Republic had the highest proportion of patients

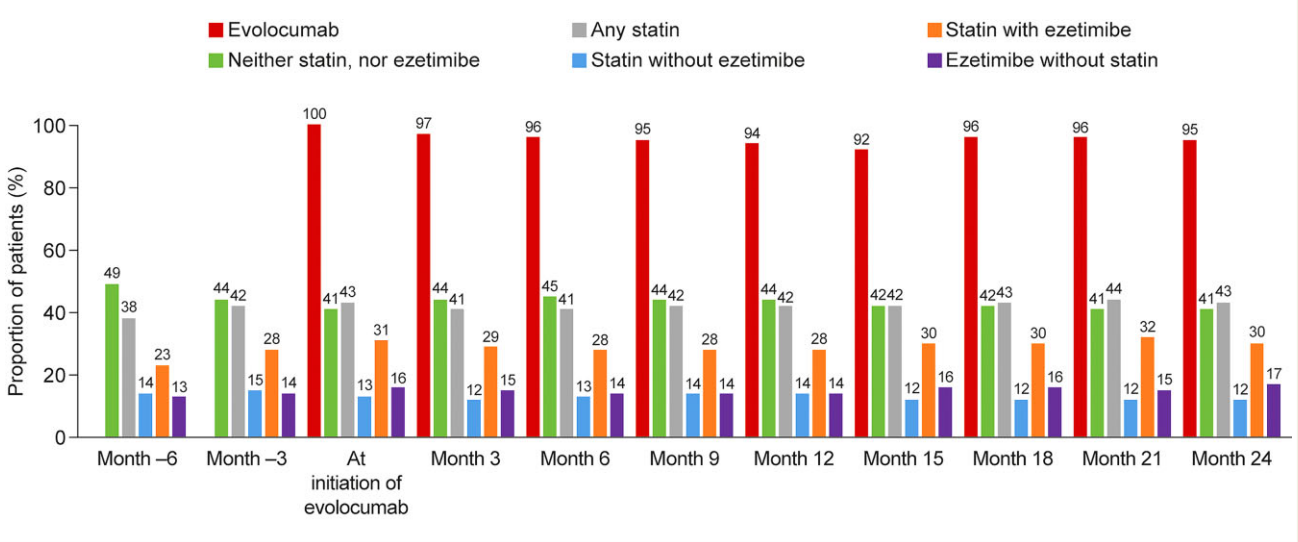


Figure 2 Lipid-lowering therapy use before and after evolocumab initiation.

without background LLT (63%) (Supplementary material online, *Figure S2*).

The proportion of patients on evolocumab at each 3-month follow-up window up to 24 months ranged from 92% to 98%, of which most patients received evolocumab 140 mg subcutaneously every 2 weeks. The proportion of patients who reported missing any evolocumab dose each month was minimal (0.12–0.98%). At the time of this interim analysis, 128 patients (7%) had documented that they permanently discontinued evolocumab.

Overall patient-reported ADRs and ADRs related to discontinuation of evolocumab are described in the Supplementary material (Supplementary material online, *Tables S3* and *S4*).

Lipid-lowering therapy-stabilized low-density lipoprotein cholesterol levels at baseline and during follow-up

Overall, median (Q1, Q3) LDL-C at baseline was 3.98 (3.17, 5.07) mmol/L but varied across patient groups; median (Q1, Q3) LDL-C at baseline was 3.68 (2.97, 4.60) mmol/L for patients with 'ASCVD without FH', 4.00 (3.24, 5.09) mmol/L for 'ASCVD with FH', 5.22 (4.11, 6.48) mmol/L for 'FH without ASCVD', and 5.17 (4.11, 6.20) mmol/L for those in the 'neither FH nor ASCVD' group (*Figure 3*). At a country level, median (Q1, Q3) LDL-C levels at baseline ranged from 3.59 (2.98, 4.50) mmol/L in Switzerland to 5.20 (4.02, 6.61) mmol/L in Bulgaria (*Figure 4*). In most countries, LDL-C levels at evolocumab initiation were several-fold higher than guideline-recommended treatment thresholds for PCSK9i initiation (*Table 1*).

In the overall population, the median on-treatment LDL-C level decreased by 58.1% (95% CI 41.4–70.9), with a corresponding absolute LDL-C reduction of 2.22 mmol/L (1.56–2.94) within 3 months of evolocumab initiation; this reduction was maintained over 24 months. At a country level, within 3 months of evolocumab initiation, the decrease in median LDL-C levels ranged from 53% (Germany) to 68% (Belgium) (*Figure 4*), with corresponding absolute LDL-C reductions of 1.91–2.99 mmol/L (Supplementary material online, *Figure S3*). Median LDL-C levels at 3 months were closer to guideline-recommended treatment thresholds in those countries with lower reimbursement criteria (Supplementary material online, *Figure S4*).

European Society of Cardiology/European Atherosclerosis Society low-density lipoprotein cholesterol goal attainment

In the overall population, 1753 patients with data available for assessment of LDL-C goal attainment at data cut-off for this interim analysis (31 July 2020) were stratified based on individual CV risk. Of these, 1626 (93%) were classified as very high risk and 127 (7%) were classified as high risk with at least one post-baseline LDL-C measurement. Overall, 58% (95% CI 56.1–60.7) of patients achieved their risk-based LDL-C goal at least once during follow-up. The respective numbers for very high-risk and high-risk patients were 59% (95% CI 56.3–61.0) and 55% (95% CI 46.4–63.5) (*Figure 5A*). For both groups, goal attainment was higher for those receiving background LLT at evolocumab initiation: 68% (95% CI 65.2–71.0) and 72% (95% CI 61.0–80.9) for very high risk and high risk, respectively, vs. corresponding figures of 45% (95% CI 40.8–48.4) and 31% (95% CI 19.9–44.3) for those without background LLT. A similar pattern was observed in all subgroups whereby goal attainment was higher in patients who received background LLT than those who did not, in both the high-risk and very high-risk groups. Goal attainment was the lowest in the 'FH without ASCVD' group at very high risk compared with the other two groups; however, this group had a higher baseline LDL-C (*Figure 5A*).

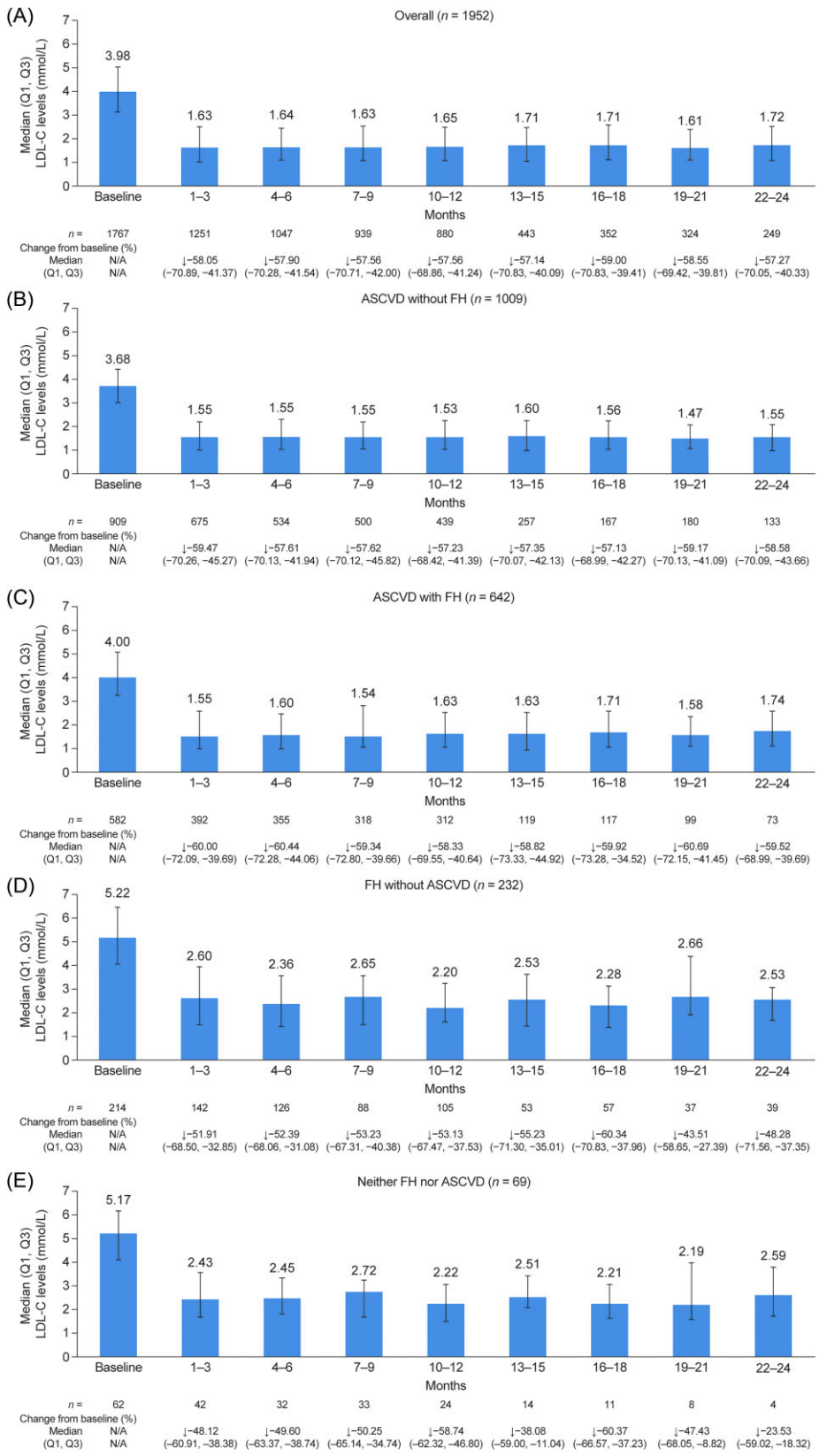


Figure 3 Low-density lipoprotein cholesterol levels at baseline and up to 24 months after evolocumab initiation in (*A*) the overall population and patients in the (*B*) 'ASCVD without FH', (*C*) 'ASCVD with FH', (*D*) 'FH without ASCVD', and (*E*) 'neither FH nor ASCVD' groups. The numbers of patients at baseline are lower than the overall/total subgroup populations because baseline low-density lipoprotein cholesterol measurements were not available for all patients. ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; NA, not applicable and LDL-C, low-density lipoprotein cholesterol.

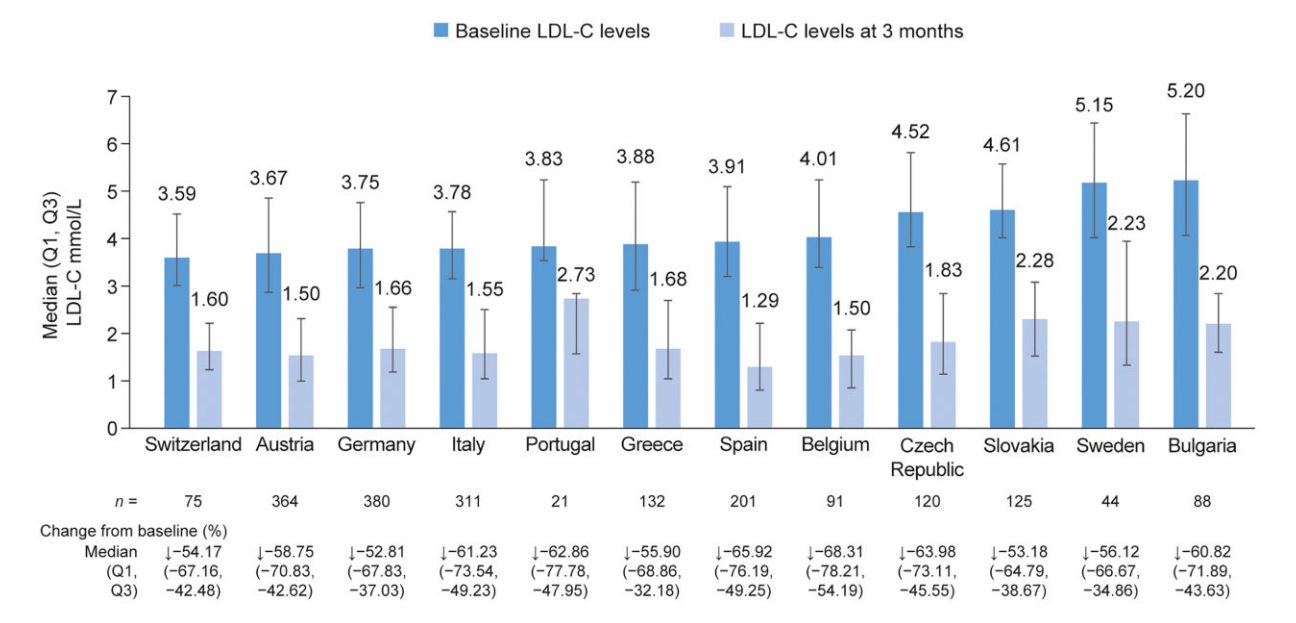


Figure 4 Low-density lipoprotein cholesterol levels at baseline and at 3 months after evolocumab initiation by country. LDL-C, low-density lipoprotein cholesterol.

Risk-based goal attainment by country is shown in *Figure 5B*; this ranged from 35% (95% CI 22.4–49.8) in Sweden to 71% (95% CI 60.0–80.3) in Belgium.

Simulated cardiovascular risk reduction

Of the 1009 patients in the 'ASCVD without FH' group, the potential CV risk reduction after evolocumab treatment could only be simulated in 730 patients owing to missing data. The predicted and simulated 10-year CV risk before evolocumab treatment in this group ranged from a median (Q1, Q3) of 34% (24–46%) to 40% (32–50%) across all three methods, with simulated RRR of 34% (24–44%). The calculated ARR ranged from 9% (6–14%) to 11% (7–16%), with NNT between 9 and 11 to prevent one additional CV event over 10 years (Supplementary material online, *Table S5*). The simulated probability distributions of 10–year CV risk before and after evolocumab treatment, using the three different methods for predicting and simulating CV risk before evolocumab treatment, are shown in *Figure 6A*. Probability distributions for 10-year ARR using the three different methods for predicting and simulating 10-year CV risk before evolocumab treatment are presented in *Figure 6B*.

Of the 232 patients in the 'FH without ASCVD' group, the 10-year CV risk before evolocumab using SAFEHEART could only be predicted in 203 patients owing to missing data. The median (IQR) baseline 10-year CV risk was 3% (2–4%). Given uncertainties regarding the low estimated baseline risk in an otherwise high-risk population, CV risk reduction simulations were not performed in this group.

Discussion

This study represents the largest multicountry registry of PCSK9i use in routine clinical care settings to date. It provides a unique opportunity to systematically assess the characteristics of those receiving evolocumab, the patient populations in which PCSK9is are used, and potential benefits of LDL-C lowering on CV risk through simulation. Our findings demonstrate that evolocumab was used predominantly in those with ASCVD or patients with FH who are treated as a primary prevention patient. Patients categorized as 'neither FH nor ASCVD' reported high LDL-C levels (>5 mmol/L), indicating that these patients may have had FH, polygenic hypercholesterolaemia, or mixed dyslipidaemia. The patients in this study reflect the clinical characteristics of those identified in dyslipidaemia guidelines (i.e. individuals with a high unmet need, at high risk, and in whom PCSK9i therapy may be effective despite maximally tolerated oral LLT). However, the median baseline LDL-C levels at evolocumab initiation were about triple the guideline recommendations and varied from country to country, in part reflecting the different LDL-C thresholds mandated for reimbursement of PCSK9is. In this real-world study, evolocumab therapy was associated with a reduction in LDL-C of ~60% and this reduction was maintained over 24 months, providing real-world validation of prior observations from randomized trials.[5,17] Evolocumab was well tolerated, with effectiveness and safety comparable with previously reported randomized controlled trials.[5,17]

The HEYMANS study offers potential solutions to the implementation gaps highlighted in the EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care (DA VINCI) study, which described the contemporary use of LLT and goal attainment in patients across 18 European countries.[9] In the DA VINCI study, most patients received statin-based monotherapy (84%) with little use of combination therapy, 9% of patients received statins and ezetimibe, and 1% received a PCSK9i in conjunction with an oral LLT. In DA VINCI, it was demonstrated that even when statin intensity was optimized, only ~20% of those on high-intensity statins alone achieved an LDL-C level

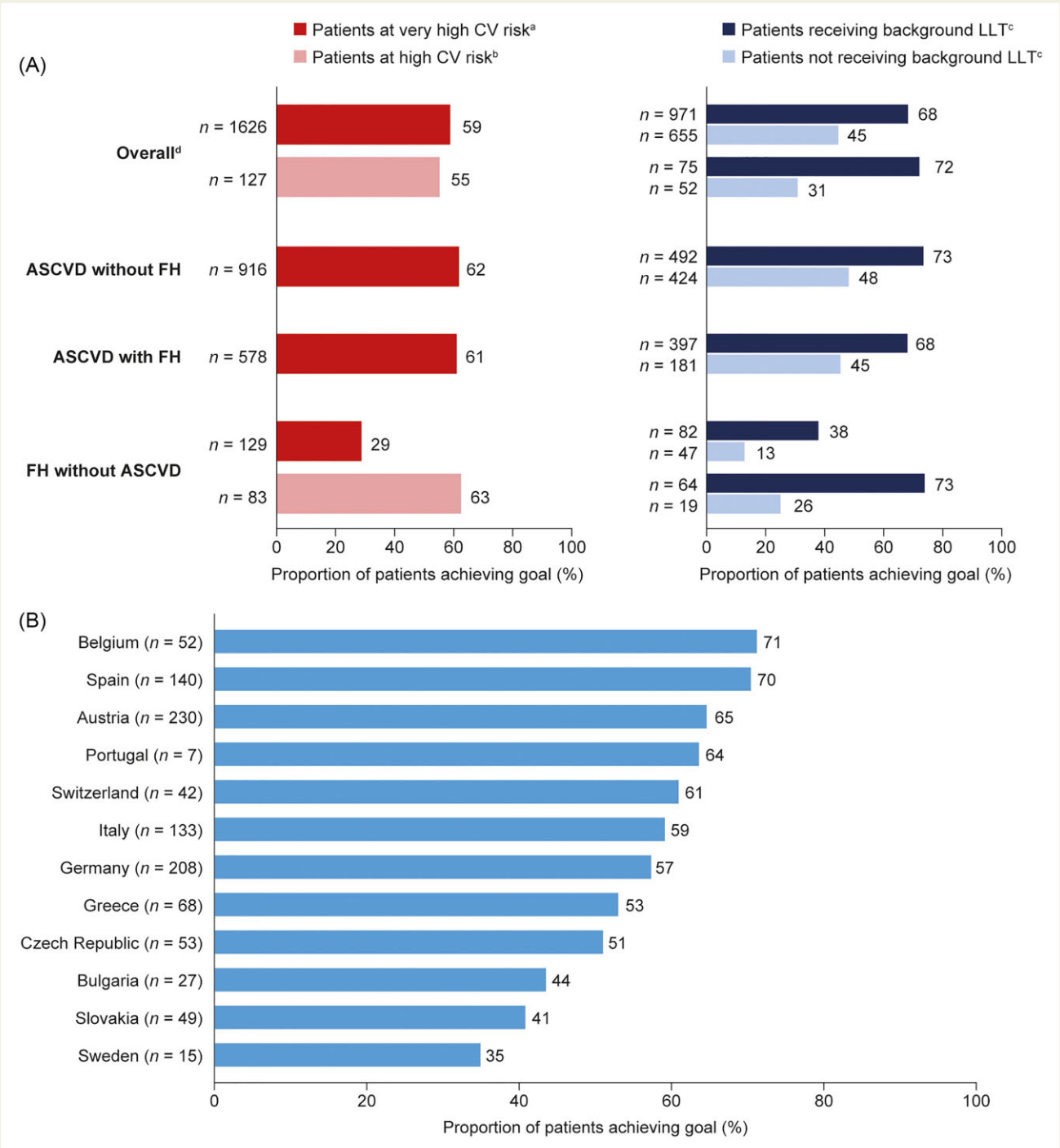


Figure 5 Risk-based low-density lipoprotein cholesterol goal attainment (*A*) by subgroup and (*B*) by country. In (*A*), *n* represents the total number of patients and in (*B*) *n* represents the number of patients achieving their low-density lipoprotein cholesterol goal. At data cut-off for this interim analysis (31 July 2020), 1753 patients had data available for assessment of low-density lipoprotein cholesterol goal attainment. Patients were included in the analysis if they had at least one post-baseline low-density lipoprotein cholesterol value and were classified as high or very high risk according to the European Society of Cardiology/European Atherosclerosis Society guidelines. [a]Patients at very high cardiovascular risk had a low-density lipoprotein cholesterol goal of <1.4 mmol/L (patients in the 'ASCVD without FH' group and 'ASCVD with FH' group were all considered by definition to be at very high cardiovascular risk). [b]Patients at high cardiovascular risk had a low-density lipoprotein cholesterol goal of <1.8 mmol/L as per the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines. [c]Background lipid-lowering therapy was defined as the use of statins and/or ezetimibe at the time of initiation of evolocumab. [d]The sum of the three subgroups is not equal to the total number evaluable for low-density lipoprotein cholesterol goal attainment ($n = 1753$) because patients without familial hypercholesterolaemia or atherosclerotic cardiovascular disease were included in the overall numbers but not in the subgroups. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; and LLT, lipid-lowering therapy.

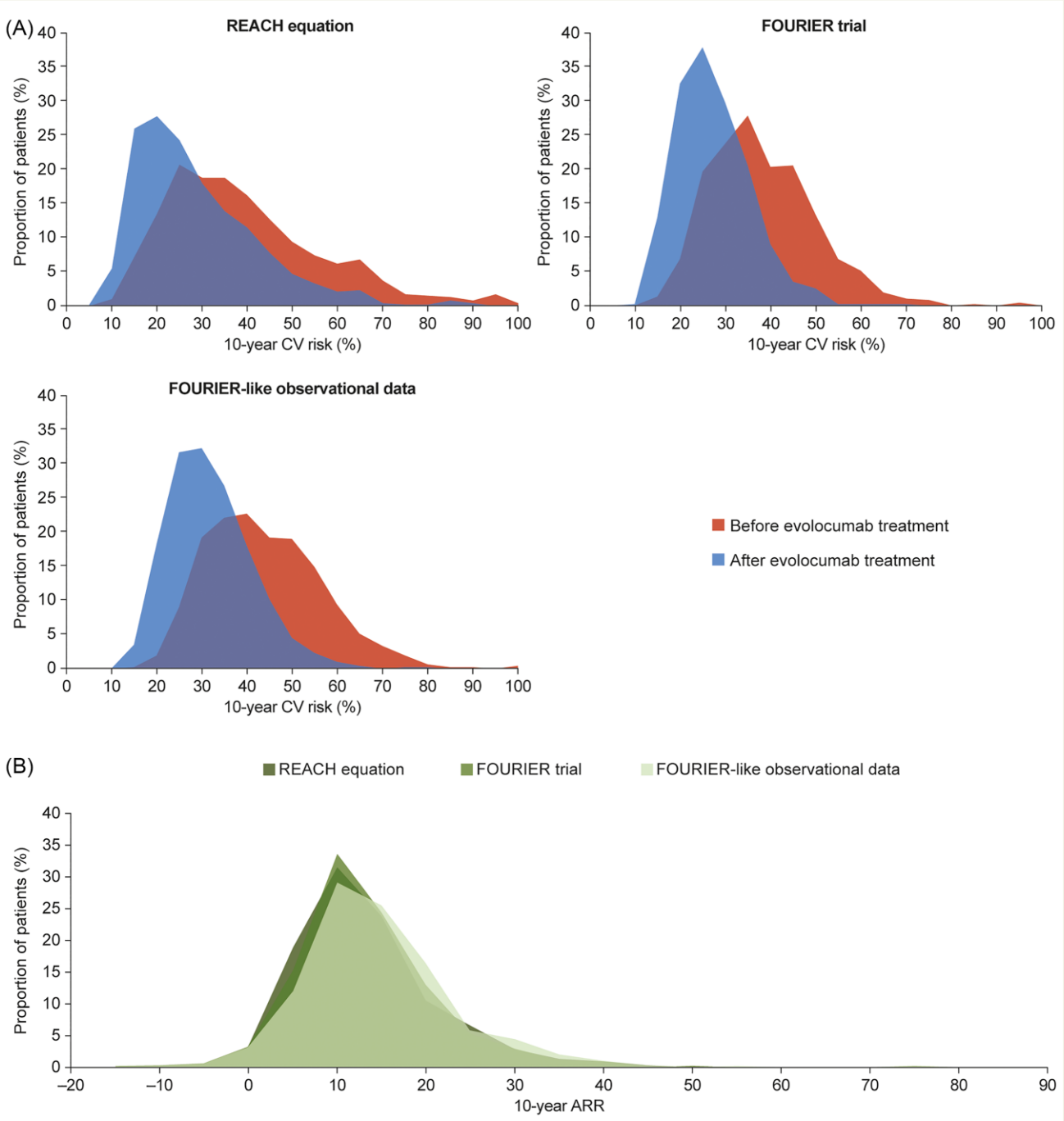


Figure 6 Simulated probability distributions for 10-year cardiovascular risk before and after evolocumab treatment (*A*) and 10-year absolute risk reduction (*B*) using three different methods for predicting and simulating 10-year cardiovascular risk in patients with atherosclerotic cardiovascular disease without familial hypercholesterolaemia. ARR, absolute risk reduction; CV, cardiovascular; FOURIER, Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; and REACH, REduction of Atherothrombosis for Continued Health.

of <1.4 mmol/L.[9] A slightly higher proportion of patients achieved an LDL-C <1.4 mmol/L when statins and ezetimibe were combined. However, 67% of patients who received a PCSK9i with an oral LLT achieved an LDL-C level <1.4 mmol/L. Taken together, these data suggest that, in order to achieve the 2019 ESC/EAS goals for those at very high risk, increased use of combination therapy is required.

These findings are consistent with findings from the SWEDEHEART post-myocardial infarction (MI) registry, a simulation study based on current practice in Sweden, which demonstrated that maximized statin therapy resulted in ~30% of patients who have previously experienced an MI attaining an LDL-C reduction of 50% or more.[18] Simulations suggested that it was likely that the majority of the re-

maining patients in SWEDEHEART would achieve their LDL-C goals if PCSK9is were added as a combination therapy.[18]

In our study, LDL-C goal attainment was higher among patients receiving evolocumab and background LLT (either statins or ezetimibe or both) compared with those not receiving background LLT. In the patients receiving background LLT, 68% and 72% of patients at very high risk and high risk, respectively, achieved their LDL-C goals. In comparison, among those not receiving background LLT at evolocumab initiation, only 45% and 31% of patients at very high risk and high risk, respectively, achieved their LDL-C goals. In line with DA VINCI, data from HEYMANS therefore demonstrate that the likelihood of achieving the 2019 LDL-C goals for those at very high risk (LDL-C <1.4 mmol/L) is increased when PCSK9is are used in combination with oral LLT.

In our study, patients who received evolocumab as part of routine clinical care reported baseline LDL-C levels almost three times higher than the present threshold recommended for the initiation of PCSK9is in current clinical guidelines.[4] The likely determining LDL-C level at which evolocumab is initiated is the threshold for reimbursement set by the state/insurers in individual countries. Our findings reflect the fact that reimbursement thresholds for PCSK9is in most countries are much higher than those recommended in clinical guidelines, highlighting the large disparity between current local reimbursement criteria and European guidelines. Furthermore, there were differences between countries in the reimbursement threshold for PCSK9i use, which impacts the type of patients offered therapy. This is supported by our observation of variations in LDL-C levels at evolocumab initiation between countries and differences in the proportion of patients who were not receiving any oral LLT prior to evolocumab initiation. Finally, in most countries, LDL-C levels at evolocumab initiation were even higher than the national LDL-C level required for reimbursement. Taken together, these findings indicate that a major barrier to effective implementation of ESC/EAS recommendations and thus control of LDL-C for many patients resides within the current healthcare system/care pathway structure itself.

HEYMANS is an observational study, and collection of CV outcomes was not part of the study design. Nevertheless, it is possible to assess the potential CV benefits for those who received evolocumab using risk prediction and simulation techniques to assess absolute risk prior to evolocumab initiation, and treatment benefit from the observed reductions in LDL-C through simulation analyses. In HEYMANS, the predicted absolute risk prior to evolocumab initiation was higher than the risk observed in the placebo group of the FOURIER trial.[5] This could be driven in part by the fact that, in our study, patients were enrolled who had baseline LDL-C levels almost two-fold higher than patients enrolled in the FOURIER trial.[5] Additionally, as often observed in registries or real-world studies, patients receiving treatments outside of the setting of trials have significantly more comorbidities and risk factors, which contribute to a higher CV risk. The predicted absolute benefit from our modelling of the HEYMANS population was larger than the observed absolute benefits in the FOURIER trial,[5] suggesting that when used in clinical practice, PCSK9is offer substantial health benefits. As the relative reduction in risk is proportional to absolute lowering of LDL-C, irrespective of how it is achieved, it follows that greater RRR benefits would be derived from combination therapy rather than monotherapy. For those at highest risk, an indirect effect of recommending a lower LDL-C goal is to provide greater absolute LDL-C lowering. However, the current large gap that exists between patients eligible for PCSK9is and those who ultimately receive them in clinical practice suggests that the potential of these potent therapies to impact the burden of CV disease in Europe is not being optimized.

The current limited use of PCSK9is reflects uncertainties among clinicians regarding reimbursement, particularly those not working in a specialized lipid setting. Facilitating access to PCSK9is requires less complicated local regulations than the existing criteria. Our findings suggest that a re-evaluation of the present reimbursement criteria for PCSK9is is required in Europe. Lowering the LDL-C threshold for PCSK9i reimbursement could have important benefits for population health. It would result in additional patients who are receiving oral LLT therapies being eligible for PCSK9is, thus affording them the opportunity to benefit from combination and not evolocumab monotherapy. As recently recommended by the EAS,[19] increased and immediate use of fixed-combination therapy in very high-risk patients, together with facilitated access to PCSK9is, would ultimately result in increased achievement of the current ESC/EAS guidelines. What is certain, however, is that, based on the current reimbursement criteria and LDL-C levels in Europe, there will continue to be a significant gap between guideline recommendations and their implementation into clinical practice if countries continue to rely on a statin monotherapy-based approach. As doubling the statin dose results in ~6–8% further LDL-C lowering, an approach of high-intensity statins for all will not abolish this gap.[20] Thus, the clinical approach to LLT use should follow the lessons of the hypertension field and its approach to blood pressure lowering, which does not rely on a single therapy but rather combinations of different treatments.[21]

Our study has several limitations, which merit consideration. Due to the observational nature of the study, potential misclassifications of data may have occurred. In addition, data were not collected regarding the proportion of patients who were poor responders, the proportion of patients who needed LLT after initiation of evolocumab, or the proportion of patients who tolerated statins after being categorized as statin intolerant. Furthermore, physicians' choice of LLT and local prescribing restrictions may have affected observations regarding risk-based LDL-C goal attainment by country. Participating sites may reflect enthusiastic and more interested healthcare professionals, so it is possible that the observations outside of the current participating sites could be worse or better. Finally, a simulation approach was used to infer potential CV risk reduction benefits of evolocumab, and collection of CV outcome data would have strengthened our study.

Conclusions

In European clinical practice, evolocumab therapy was associated with a reduction in LDL-C levels of ~60%; this reduction was maintained over 24 months, potentially reducing CV risk. More patients attained risk-based LDL-C goals when receiving evolocumab in combination with LLT vs. those not receiving combination therapy. Overall, patients initiated on evolocumab had baseline LDL-C levels three times higher than the present threshold for PCSK9i use

recommended in the ESC/EAS guidelines, largely reflecting disparities between implementation and guidelines. Lowering the LDL-C threshold for PCSK9i reimbursement would allow more patients to receive combination therapy, increasing the likelihood of patients at highest CV risk achieving their recommended ESC/EAS LDL-C goals.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

Funding

Amgen (Europe) GmbH.

Acknowledgements

The authors would like to thank Sinéad Flannery, PhD, of PharmaGenesis London, London, UK, and Ryan Woodrow of Aspire Scientific, Bollington, UK, for medical writing support. K.K.R. acknowledges support by the NIHR Imperial Biomedical Research Centre and from the NIHR ARC for north-west London. The authors would like to thank all the investigators and patients. A full list of HEYMANS investigators can be found in the Supplementary material online, *Appendix*.

Conflict of interest: K.K.R. reports grants from Amgen during the conduct of the study; personal fees from AbbVie, Aegerion, Akcea, Algorithm, AstraZeneca, Bayer, Boehringer Ingelheim, Cerenis, Cipla, Dr Reddys, Esperion, Kowa, Lilly, Novartis, Silence Therapeutics, Takeda, The Medicines Company, and Zuelling Pharma; and grants and personal fees from Amgen, Daiichi Sankyo, MSD, Sanofi–Regeneron, and Pfizer, outside the submitted work. N.D. is an employee of Amgen Ltd and stockholder of Amgen. M.S. is an employee of Amgen (Europe) GmbH and stockholder of Amgen. I.B. is an employee of Amgen Ltd and stockholder of Amgen. C.E. reports grants and personal fees from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Novo Nordisk, and Sanofi. P.P.F. reports consulting and speaker's fees from Amgen. G.V. is an employee of Amgen (Europe) GmbH and stockholder of Amgen. A.V. reports grants from Amgen, Novartis, and Sanofi–Regeneron, and personal fees from Aegerion, Akcea, Amgen, Amryt, Daiichi Sankyo, Novartis, and Sanofi–Regeneron. E.B. reports consulting fees from Aegerion, Akcea, Amarin, Amgen, Genfit, Ionis Pharmaceuticals, Lilly, MSD, Mylan, Regeneron, Rottapharm–MEDA, Sanofi, Servier, and Unilever.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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