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ORIGINAL RESEARCH

Evolocumab-Based LDL-C Management in High and Very High Cardiovascular Risk Patients in German Clinical Practice: The HEYMANS Study

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ABSTRACT

Introduction: Low-density lipoprotein cholesterol (LDL-C) is among the most important modifiable risk factors for cardiovascular disease. In very high-risk patients, the European Society of Cardiology/European Atherosclerosis Society guidelines recommend attaining LDL-C < 55 mg/dL. In the German cohort of the observational HEYMANS study, we aimed to describe the clinical characteristics and LDL-C control among patients initiating evolocumab.

Methods: Data was collected between 09/2016 and 05/2021 for ≤ 6 months before (retrospectively) and ≤ 30 months after evolocumab initiation (prospectively). Patient characteristics, lipid-lowering therapy (LLT), lipid values, evolocumab use, and safety were collected.

Prior presentation: Data from the German cohort of HEYMANS have been presented as an abstract and poster at the 2022 annual congress of the German Society of Cardiology (Deutsche Gesellschaft für Kardiologie–DGK; https://dgk.org/kongress_programme/ht2022/abstracts/aP340.html).

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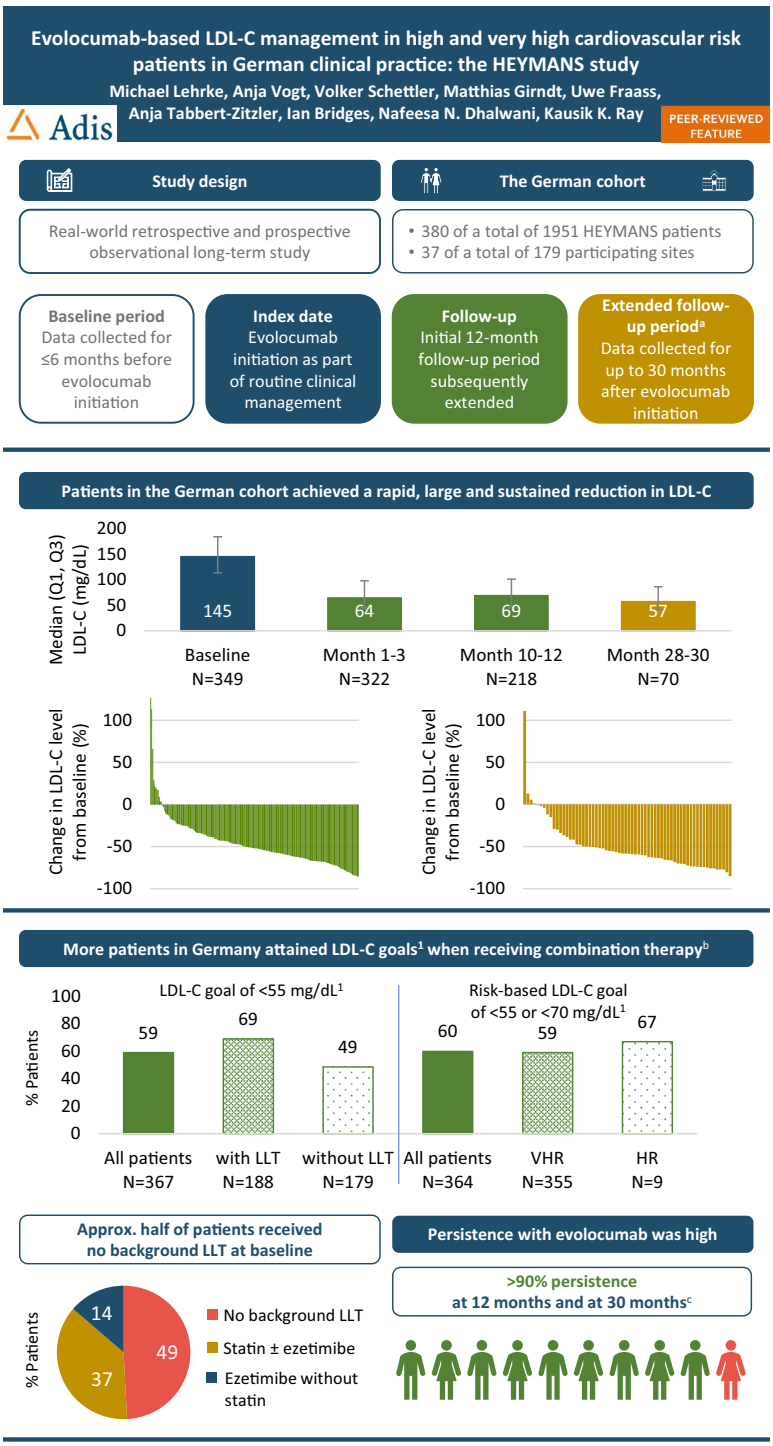
Results: Of 380 enrolled patients, 93% received evolocumab in secondary prevention and 69% had a history of statin intolerance. At study baseline, 49% did not receive any statins and LDL-C was very high (145 mg/dL). Use of evolocumab decreased LDL-C by a median of 53% within 3 months and remained stable thereafter, despite mainly unchanged background LLT. Overall, 59% attained an LDL-C level < 55 mg/dL (69% with, 49% without LLT). Persistence to evolocumab was 90.6% in months 1–12 and 93.5% in months 13–30. Adverse drug reactions were reported in 8% of patients.

Conclusion: Data from the German HEYMANS cohort corroborate previous reports on evolocumab effectiveness and safety in clinical practice. Evolocumab initiation was associated with a rapid and sustained LDL-C reduction. Persistence with evolocumab was high. Our finding that patients receiving an evolocumab/LLT combination are more likely to attain the LDL-C goal than those receiving evolocumab alone corroborates previous data showing the importance of using highly intensive therapy. Graphical abstract available for this article.

Trial Registration: ClinicalTrials.gov Identifier NCT02770131 (registration date 27 April 2016).

Graphical Abstract:



1. Mach F, et al. Eur Heart J 2020;41(1):111-8. [a] Only patients still on study at the time of approval of the protocol amendment were allowed to continue into the extended follow-up period. [b] Compared to those who received evolocumab alone. [c] The percentage at month 30 is based on patients who entered the extended follow-up period. HR, high cardiovascular risk; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; VHR, very high cardiovascular risk.

The graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, and copyright information, please see the full text online.

Keywords: Evolocumab; PCSK9 inhibitors; LDL-C; Registry; Guidelines; Cardiovascular risk

Key Summary Points

Why carry out this study?

Low-density lipoprotein cholesterol (LDL-C) is among the most important modifiable risk factors for cardiovascular disease.

While the clinical effectiveness of evolocumab in lowering LDL-C and reducing cardiovascular risk has been established in randomized controlled trials, the characteristics of patients receiving evolocumab in clinical practice depends on country-specific reimbursement criteria.

The observational HEYMANS study aimed to describe the clinical characteristics and LDL-C control among patients initiating evolocumab.

What was learned from the study?

Data from the German HEYMANS cohort show that evolocumab initiation was associated with a rapid and sustained LDL-C reduction, and patients receiving a combination of evolocumab with statins and/or ezetimibe were more likely to attain the LDL-C goal than those receiving evolocumab alone.

Persistence with evolocumab was high throughout the study period.

Our findings corroborate previous reports on evolocumab effectiveness and safety in clinical practice and support the use of highly intensive therapy.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24657735.

INTRODUCTION

Cardiovascular diseases (CVD) are among the key drivers of mortality in Germany and worldwide, and a major contributor to morbidity and disability [1–4]. High levels of low-density lipoprotein cholesterol (LDL-C) ranked third among the most important modifiable risk factors for CVD in 2019 after high systolic blood pressure and dietary risks [2]. In patients with high or very high cardiovascular risk, the active management of dyslipidemia is recommended by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) to lower LDL-C by $\geq$ 50% from untreated levels and attain risk-based LDL-C goals of $<$ 70 mg/dL ($<$ 1.8 mmol/L) or $<$ 55 mg/dL ($<$ 1.4 mmol/L), respectively [5]. The DA VINCI study showed that, especially in very high-risk patients, intensification of treatment to the highest tolerated statin dose and through initiating combination therapy by adding ezetimibe and finally a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor increased LDL-C goal attainment [6, 7]. This stepwise treatment intensification to include PCSK9 inhibitors in patients who do not reach the recommended LDL-C goals with maximally tolerated statin doses and/or ezetimibe is also recommended by the ESC/EAS guidelines [5, 8].

The choice of treatment and thus treatment intensification is commonly governed by local reimbursement criteria, whereby insufficient lowering of LDL-C using statins and/or ezetimibe over a certain period of time and documented intolerance to statins are common criteria for reimbursement of PCSK9 inhibitors. Consistent with scientific evidence, guideline-recommended LDL-C goals have become more stringent over time [5, 9, 10] and clinical practice should evolve over time to meet those targets. In Germany, however, a survey from 2023 showed that only 19.3% of physicians self-reported to fully adhere to the 2019 ESC/EAS guidelines and more than 80% of the surveyed

physicians reported an LDL-C target failure rate of at least 30% in high-risk patients [11]. According to the SANTORINI study [12], the use of combination therapies has increased compared with earlier studies such as DA VINCI [6, 7], EUROASPIRE [13], or DYSIS II [14] but remains inadequate in regards to the standards of the 2019 ESC/EAS guidelines.

At present, evolocumab is reimbursed in Germany in individuals with heterozygous familial hypercholesterolemia (FH) or non-FH or mixed dyslipidemia with diagnosed CVD and additional risk factors for cardiovascular events who did not attain LDL-C goals over the course of 12 months under diet and using other lipid-lowering agents (statins, anion-exchange resins, cholesterol absorption inhibitors, adenosine triphosphate-citrate lyase [ACL] inhibitors) [15]. Exceptions to the 12-month rule are granted in justified and well-documented cases, e.g., in the post-acute coronary syndrome (ACS) setting or in patients with rapidly progressing atherosclerotic disease.

The effectiveness of evolocumab was shown in the "cHaractEristics of hYperlipidaeMic pAtieNts at initiation of evolocumab and treatment patternS" (HEYMANS) study from a large registry of evolocumab-treated patients across 12 European countries (Austria, Belgium, Bulgaria, Czech Republic, Germany, Greece, Italy, Portugal, Slovakia, Spain, Sweden, and Switzerland), based on the LDL-C status collected prior to evolocumab initiation (≤ 6 months) and during evolocumab treatment over a maximum follow-up period of 30 months [16, 17]. Across all participating countries the study protocol, methods, and statistical analyses were identical. HEYMANS aimed to describe the clinical characteristics of patients at initiation of evolocumab and the parameters associated with clinical management of hyperlipidemia in patients initiated on evolocumab treatment in routine clinical practice. Data from the German HEYMANS cohort are reported here with special consideration of local clinical practice.

METHODS

A detailed description of the HEYMANS study methods has been previously published [16]; a brief summary is provided here.

Study Design and Patient Population

HEYMANS was an observational cohort study comprising a retrospective period of ≤ 6 months, the time point of evolocumab initiation (study baseline), and a prospective follow-up period of ≤ 30 months. The initially planned duration of follow-up was 12 months which was extended to 30 months in a protocol amendment from February 2018. Only patients who had not completed the 12-month observation by the date of the protocol amendment could be included in the extended follow-up period. In the German cohort, the first patient was enrolled on 28 September 2016 and the study ended on 17 May 2021.

The study enrolled adult patients (≥ 18 years) receiving evolocumab according to local reimbursement criteria in force at the time. Patients were enrolled after initiating evolocumab and evolocumab was prescribed independently of study inclusion. Use of a PCSK9 inhibitor within 12 weeks before evolocumab initiation, either in the setting of an interventional study or in routine clinical practice, was an exclusion criterion.

Outcome Variables

Demographics, disease characteristics, cardiovascular risk factors, lipid profiles, and prior/current lipid-lowering therapy (LLT) use were collected at the time of initiation of evolocumab; subsequent lipid profiles, as well as the use of background LLT (i.e., a statin, ezetimibe, or a combination thereof) and evolocumab were documented as per routine clinical practice.

LDL-C response parameters over time, i.e., median LDL-C levels and percentage reduction from study baseline, were assessed in all patients and were summarized at each 3-month interval. Waterfall plots displaying the on-treatment percentage change in LDL-C levels from study

baseline for the periods of 1–3, 10–12, and 28–30 months were prepared to illustrate the variation of LDL-C in individual patients.

The proportion of patients attaining a ≥ 50% LDL-C reduction from the study baseline value at least once during follow-up was assessed. LDL-C goal attainment was estimated as the proportion of patients attaining an LDL-C level < 55 mg/dL or < 70 mg/dL, in line with the 2019 ESC/EAS dyslipidemia guidelines [5], at least once during the entire follow-up. Although patient enrollment started prior to the 2019 issuance of the ESC/EAS guidelines, the study duration including the follow-up period of 30 months allowed for treatment to be adapted and stabilized according to the standards recommended in the 2019 guidelines.

Persistence was defined as the proportion of patients continuing to receive evolocumab in the study at a specified time point. Those who stopped the study before this time point but who were still receiving evolocumab were excluded from the persistence analysis. Patients were considered to have discontinued evolocumab if they stopped therapy during the observation period. Evolocumab persistence was analyzed separately for two time periods: 0–12 months and 12–30 months.

Statistical Analysis

Descriptive summary statistics were reported. Categorical data were summarized as frequencies and percentages. Continuous data were reported as mean and standard deviation (SD) or median and first and third quartile (Q1, Q3). When appropriate, 95% confidence intervals (CI) were produced. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Ethical Statement

The study was performed in accordance with the Declaration of Helsinki and the guidelines of the International Council for Harmonization. The study was registered in ClinicalTrials.gov (Identifier NCT02770131). The study protocol and the protocol amendments were approved by the institutional ethics committees of each participating study center (Supplemental Table S1); the ethics committee of the Bavarian state medical association acted as the lead ethics committee for the German sub-study of HEYMANS (study reference number 16030). All patients or their legally acceptable representatives provided written informed consent before participation in this study.

RESULTS

Patient Disposition

In Germany, 37 study centers enrolled a total of 380 patients and 361 completed 12 months of observation; 147 patients entered the extension phase and 138 completed 30 months of observation (supplemental Fig. S1). The median (Q1, Q3) duration of follow-up was 12.0 (12.0, 30.0) months.

Patient Characteristics

Baseline and clinical characteristics are shown in Table 1. The majority of patients were male and with a mean (SD) age of 61.5 (10.4) years. Almost all patients had a prior cardiovascular event (92.9%, $n = 353$) and were, therefore, receiving evolocumab in secondary CVD prevention. Supplemental Table S2 provides details on the history of cardiovascular disease. Intolerance to any statin, defined as having a history of muscle-related or non-muscle-related intolerance to any statin, was reported in 69.2% ($n = 263$) of patients.

Dyslipidemia Management

The use of evolocumab and background LLT use over time is described in Fig. 1. Before evolocumab initiation (− 6 months), 59% of patients ($n = 224$) were not receiving any background LLT. At evolocumab initiation, 49% of patients ($n = 187$) did not receive background LLT. At study baseline, there was no difference between women (52%) and men (50%) in the use of statin and/or ezetimibe, or in those using high-

Table 1 Baseline and clinical characteristics of patients who initiated evolocumab

	All patients (*N* = 380)
Male	240 (63.2)
Age, years, mean (SD)	61.5 (10.4)
LDL-C level, mg/dL, median (Q1–Q3)	145 (113–184)
Hypertension	298 (78.4)
Current or former smoker	199 (52.4)
Body mass index[a]	
< 20 kg/m^2	4 (1.1)
≥ 20 kg/m^2 and < 30 kg/m^2	261 (68.7)
≥ 30 kg/m^2	107 (28.2)
Type 2 diabetes mellitus	96 (25.3)
Chronic kidney disease	61 (16.1)
Statin intolerance[b]	263 (69.2)
FH	127 (33.4)
Previous CV event	353 (92.9)
Previous ACS[c]	155 (40.8)
CAD or angina[d]	250 (65.8)
PAD	71 (18.7)
Ischemic stroke	18 (4.7)
Critical limb ischemia	12 (3.2)
Carotid artery disease	141 (37.1)
TIA	14 (3.7)
Coronary thrombosis[e]	65 (17.1)

Data are *n* (%) unless otherwise specified

ACS acute coronary syndrome, *CAD* coronary artery disease, *CV* cardiovascular, *FH* familial hypercholesterolemia, *HDL-C* high-density lipoprotein-cholesterol, *LDL-C* low-density lipoprotein-cholesterol, *PAD* peripheral artery disease, *Q* quartile, *SD* standard deviation, *STEMI* ST-elevation myocardial infarction, *TIA* transient ischemic attack

[a]Body mass index measurements were not available for all patients

[b]Statin intolerance was defined as having a history of muscle-related or non-muscle-related intolerance to any statin

[c]Previous ACS is a history of ACS, STEMI, or non-STEMI

[d]CAD or angina is a history of CAD or stable angina

[e]Coronary thrombosis (acute or non-acute) is counted as one prior CV event

intensity statin (women, 16%; men, 17%), or statin + ezetimibe (women, 24%; men, 22%). The use of background LLT was generally stable over the period of observation: At each 6-month time point, 45–54% of patients were not receiving background LLT, 35–45% of patients were receiving a statin and/or ezetimibe, and 10–14% of patients were receiving ezetimibe without a statin.

Evolocumab use remained high over time. Of the 380 patients, 36 (9.5%) discontinued evolocumab before the end of the observation period: 19 (5.0%) due to an adverse drug reaction, 5 (1.3%) each were either due to requirement for an alternative therapy, patient request, or "other" reason, and 2 (0.5%) died. Persistence to evolocumab was 90.6% ($n = 336/371$) in the first 12 months and 93.5% ($n = 130/139$) at 13–30 months; supplemental Fig. S1 shows patients' treatment status and evolocumab discontinuation in each study period.

LDL-C Levels Over Time

The median (Q1, Q3) LDL-C level at study baseline was 145 (113–184) mg/dL and was higher for women (162 mg/dL) than for men (141 mg/dL). Within the first 3 months of evolocumab treatment, LDL-C was reduced by a median (Q1, Q3) of 53% (37%, 68%; 47% [28%, 64%] in women versus 56% [42%, 70%] in men) and this reduction remained stable over the study observation period of 30 months. The median LDL-C during observation ranged between 57 and 69 mg/dL (Fig. 2). More than 50% of patients achieved a $\geq 50\%$ LDL-C reduction during their treatment with evolocumab (Fig. S2). Figure 3 shows on-treatment percentage changes in LDL-C for patients with baseline LDL-C ≥ 70 mg/dL, suggesting that at each time point the vast majority of patients achieved a large reduction in LDL-C from study baseline.

LDL-C Goal Attainment

Overall, 59% of patients ($n = 217/367$) attained an LDL-C level < 55 mg/dL, and this proportion was higher for patients receiving evolocumab in

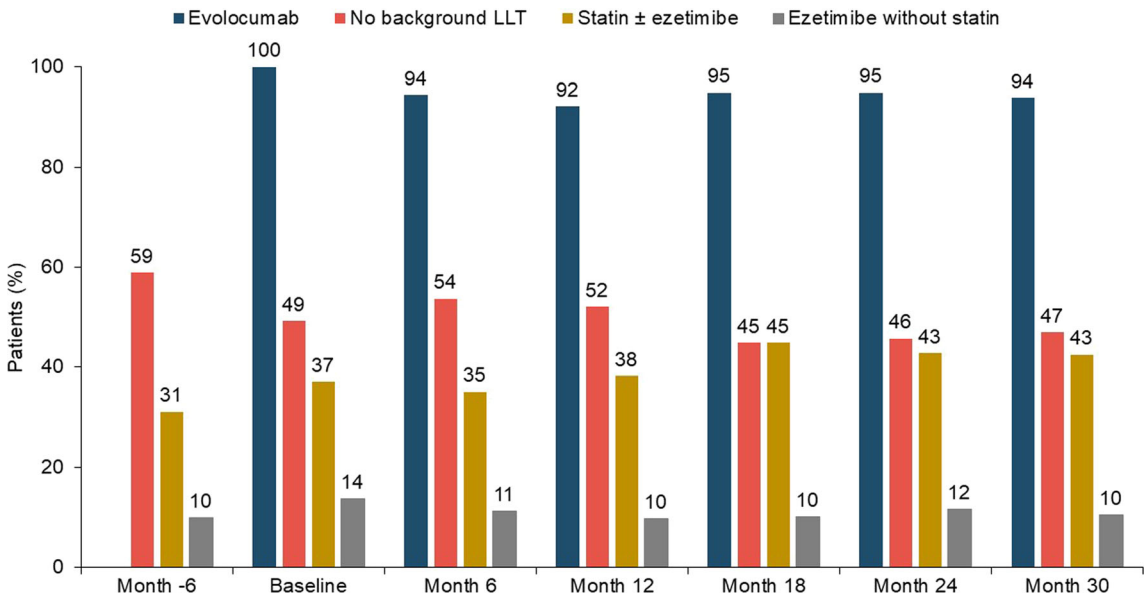


Fig. 1 Evolocumab and background LLT use over time. The term "background LLT" summarizes the use of statins and/or ezetimibe. Percentages are based on patients still in the study at the time point. Intensity of statin-based background LLT at study baseline: (i) Statin alone, $n = 54$ (15 high, 29 moderate, 10 low intensity) and (ii) Statin + ezetimibe, $n = 87$ (49 high, 24 moderate, 8 low, 6 unknown intensity). *LLT* lipid-lowering therapy

combination with background LLT (69%; $n = 130/188$) than for patients receiving evolocumab alone (49%; $n = 87/179$) (Fig. 4). Sex differences in the LDL-C goal attainment (46% of women versus 66% of men) were also observed irrespective of receiving a background LLT or not at evolocumab initiation: 59% ($n = 41/71$) and 31% ($n = 19/61$) of women with or without LLT, respectively, versus 75% ($n = 88/117$) and 58% ($n = 68/118$) of men with or without LLT, respectively. Risk-based goal attainment of < 55 mg/dL in very high-risk and < 70 mg/dL in high-risk patients was 60% ($n = 217/364$); 59% ($n = 211/355$) of very high-risk patients attained < 55 mg/dL and 67% ($n = 6/9$) of high-risk patients attained < 70 mg/dL (Fig. 4).

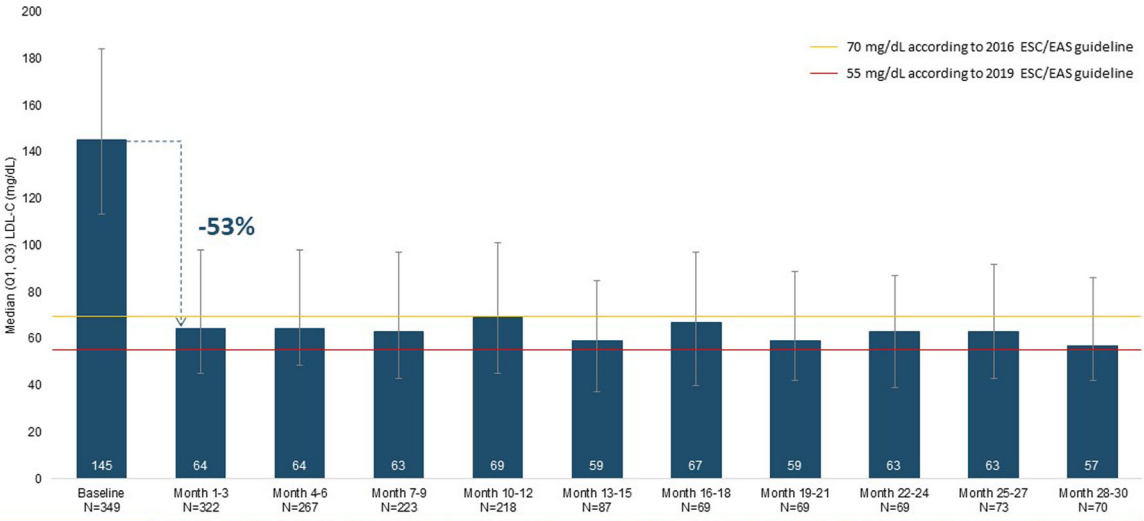
Safety

Overall, 32 patients (8%) reported non-fatal treatment-emergent adverse drug reactions. Additionally, two fatal treatment-emergent adverse events occurred (sepsis, suicide) which were not considered related to evolocumab. The most frequent event was musculoskeletal and connective tissue disorders (3%), all other treatment-emergent adverse drug reactions occurred in ≤ 1% of patients (Table 2).

DISCUSSION

The present analysis of the HEYMANS study indicates that evolocumab is used in Germany mainly in secondary prevention and often in patients with a documented history of statin intolerance. In such a cohort, an LDL-C reduction by more than 50% is recommended by the ESC/EAS guidelines [5]. In the German HEYMANS cohort, a 53% LDL-C reduction was observed within the first 3 months of evolocumab use. At any point during observation, 59% of high-risk and very high-risk patients achieved the LDL-C goal of < 55 mg/dL and 60% achieved the risk-based goal of < 55 mg/dL for very-high risk patients and < 70 mg/dL for high-risk patients.

In the German cohort of the cross-sectional DA VINCI study published in 2022, the 2019 ESC/EAS-recommended risk-based LDL-C goals



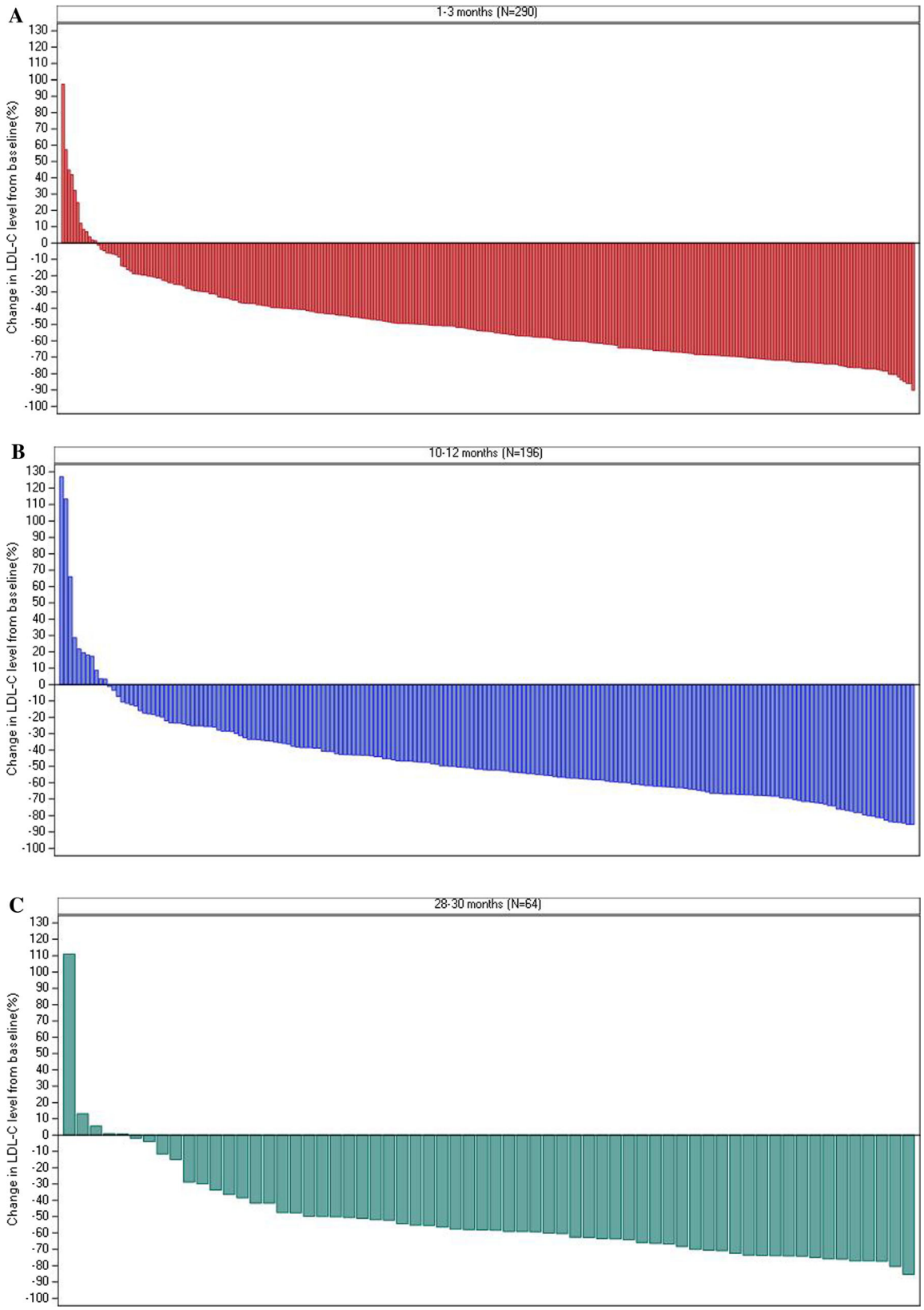
Months	Month 1-3 N=322	Month 4-6 N=251	Month 7-9 N=211	Month 10-12 N=206	Month 13-15 N=82	Month 16-18 N=64	Month 19-21 N=64	Month 22-24 N=65	Month 25-27 N=69	Month 28-30 N=66
Median (Q1, Q3) reduction from baseline (%)	↓ 53.3% (-68.4, -37.0)	↓ 53.5% (-65.6, -38.5)	↓ 54.7% (-67.7, -39.4)	↓ 51.7% (-64.0, -33.7)	↓ 55.3% (-67.6, -38.0)	↓ 55.1% (-66.2, -38.5)	↓ 56.7% (-67.1, -40.7)	↓ 56.3% (-67.4, -38.9)	↓ 56.0% (-63.5, -40.9)	↓ 58.2% (-70.0, -41.8)
Median (Q1, Q3) reduction from baseline (mg/dL)	-75.9 (-101.1, -52.0)	-79.7 (-107.0, -49.5)	-81.5 (-105.0, -50.2)	-71.0 (-97.0, -46.0)	-79.5 (-99.8, -50.0)	-83.1 -104.0, -50.0)	-84.2 (-112.1, -56.6)	-81.5 (-101.0, -49.7)	-74.0 (-106.5, -51.0)	-80.0 (-109.0, -53.4)

Fig. 2 Median (Q1, Q3) LDL-C over time. *EAS* European Atherosclerosis Society, *ESC* European Society of Cardiology, *LDL-C* low-density lipoprotein cholesterol, *Q1* lower quartile (25%), *Q3* upper quartile (75%)

[5] were attained by 28% of patients [6]. Compared with the DA VINCI study, which was conducted at a time when only very few patients were receiving a PCSK9 inhibitor, LDL-C goal attainment was markedly higher in the German HEYMANS cohort (60%). The patient cohorts, however, differed as DA VINCI was performed when patients were treated according to the less stringent 2016 iteration of the ESC/EAS guideline and with different reimbursement criteria for PCSK9 inhibitors. Additionally, 53% of the German DA VINCI patients were in primary prevention and 47% were in secondary prevention. In HEYMANS, patients were observed longitudinally for up to 30 months and the study period spanned both ESC/EAS guideline periods from 2016 to July 2019 and from August 2019 onwards. In the German HEYMANS cohort evolocumab was almost exclusively used in secondary prevention (93%). Interestingly, there were no notable changes in therapeutic standards between the 2016 and the 2019 ESC/EAS guideline periods observed in the German HEYMANS cohort, as reflected by the LDL-C levels not substantially changing over time and the background medications remaining stable.

In the present study, LDL-C was rapidly reduced by 53% within the first 3 months of evolocumab treatment. At each time point, the vast majority of patients achieved a large reduction in LDL-C from study baseline, as estimated using the waterfall plot analysis conducted in the initial 3-month period and repeated at the end of the 12-month core observation period as well as the 30-month extension period. The overall HEYMANS cohort enrolled a larger number of patients, which allowed a more in-depth sub-analysis of intra-individual LDL-C variability in 297 patients who had an LDL-C measurement at study baseline and at least one LDL-C measurement recorded within each 6-month period up until the end of follow-up at months 25–30. After an initial LDL-C reduction from study baseline, the individual LDL-C variability between follow-up visits in these patients was small [17].

In the German HEYMANS cohort, median (Q1, Q3) LDL-C level at study baseline was 145 (113–184) mg/dL, which means that 50% of patients had an LDL-C level of $\geq$ 145 mg/dL


A
1-3 months (N=290)
Change in LDL-C level from baseline(%)
B
10-12 months (N=196)
Change in LDL-C level from baseline(%)
C
28-30 months (N=64)
Change in LDL-C level from baseline(%)

◀**Fig. 3** LDL-C variability outcomes. **A** Months 1–3, $N = 290$. **B** Months 10–12, $N = 196$. **C** Months 28–30, $N = 64$. *LDL-C* low-density lipoprotein cholesterol. **A**–**C** Show on-treatment percentage change in LDL-C for patients with baseline LDL-C $\geq$ 70 mg/dL

and 25% of patients had an LDL-C level of $\geq$ 184 mg/dL. The median LDL-C at study baseline was thus almost three times the LDL-C threshold recommended by guidelines. Patients with very high initial LDL-C levels may need more intensive treatment to attain the recommended LDL-C goals despite the rapid relative reduction in LDL-C observed in the HEYMANS study. It is therefore important to identify patients at risk and intensify their treatment early on. Especially in the German HEYMANS cohort, most patients had a prior cardiovascular event with prior indication for intensive LDL-C lowering. The benefit of early LDL-C intervention was recently demonstrated in the FOURIER open-label extension (OLE) study [18]. At the end of the FOURIER trial, patients from the placebo arm were allowed to cross over to evolocumab treatment (crossover group) and were compared with patients who had received continuous evolocumab treatment from start of the trial (continuous evolocumab group). While the LDL-C-lowering effects were generally consistent between both groups, earlier attainment of low LDL-C levels was observed during the follow-up period in the continuous evolocumab group and was associated with a higher cardiovascular benefit compared with the crossover group as a result of their delayed LDL-C lowering during the FOURIER trial [18]. These findings support the recommendations of the ESC/EAS dyslipidemia guidelines to monitor patients' lipid profiles closely and to intensify lipid-lowering treatment without delay by adding a PCSK9 inhibitor in all patients who are

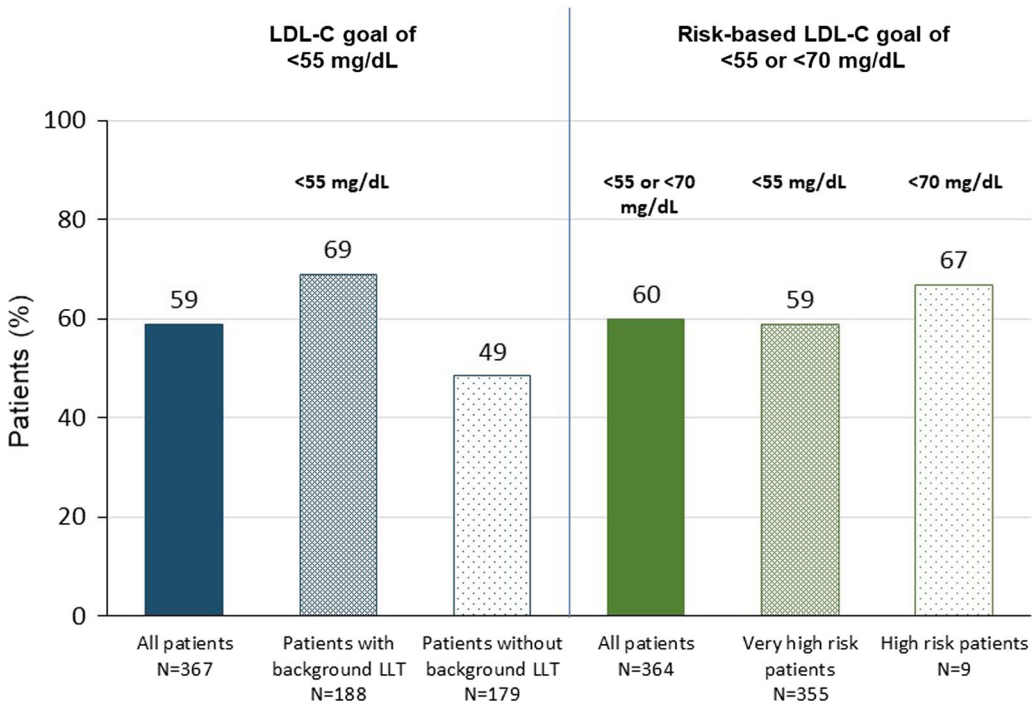


Fig. 4 Attainment of LDL-C goals. *EAS* European Atherosclerosis Society, *ESC* European Society of Cardiology, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid-lowering therapy. The 2019 ESC/EAS guidelines [5] recommend a $\geq$ 50% LDL-C reduction and the achievement of LDL-C < 55 mg/dL for patients with very high cardiovascular risk. LDL-C goal attainment data are missing for 13 patients. In the German cohort, 9 patients had a high cardiovascular risk, and 368 patients had a very high cardiovascular risk (3 patients had neither)

Table 2 Treatment-emergent adverse drug reactions reported during evolocumab therapy

System organ class Preferred term	All patients *N* = 380
Adverse drug reactions, *n* (%)	32 (8)
Ear and labyrinth disorders, *n* (%)	1 (< 1)
Vertigo	1 (< 1)
Eye disorders, *n* (%)	1 (< 1)
Dry eye	1 (< 1)
Gastrointestinal disorders, *n* (%)	4 (1)
Abdominal pain upper	2 (< 1)
Nausea	3 (< 1)
General disorders and administration site conditions, *n* (%)	4 (1)
Fatigue	2 (< 1)
Influenza-like illness	1 (< 1)
Injection site pruritus	1 (< 1)
Hepatobiliary disorders, *n* (%)	1 (< 1)
Hepatic toxicity	1 (< 1)
Infections and infestations, *n* (%)	5 (1)
Nasopharyngitis	1 (< 1)
Pharyngitis	1 (< 1)
Rhinitis	3 (< 1)
Investigations, *n* (%)	1 (< 1)
International normalized ratio decrease	1 (< 1)
Musculoskeletal and connective tissue disorders, *n* (%)	12 (3)
Arthralgia	4 (1)
Mobility decreased	1 (< 1)
Muscle spasms	1 (< 1)
Myalgia	8 (2)
Nervous system disorders, *n* (%)	5 (1)
Dizziness	2 (< 1)
Headache	3 (< 1)
Respiratory, thoracic, and mediastinal disorders, *n* (%)	2 (< 1)
Cough decreased	1 (< 1)
Productive cough	1 (< 1)
Throat irritation	1 (< 1)
Skin and subcutaneous tissue disorders, *n* (%)	5 (1)
Eczema	1 (< 1)
Hyperhidrosis	2 (< 1)
Pruritus	1 (< 1)
Rash	1 (< 1)
Vascular disorders, *n* (%)	2 (< 1)
Hypertensive crisis	1 (< 1)
Hypotension	1 (< 1)
Serious adverse drug reactions, *n* (%)	2 (< 1)
Musculoskeletal and connective tissue disorders, *n* (%)	1 (< 1)
Arthralgia	1 (< 1)
Myalgia	1 (< 1)
Vascular disorders, *n* (%)	1 (< 1)
Hypertensive crisis	1 (< 1)

unable attain their LDL-C goal using maximally tolerated doses of statin and/or ezetimibe [5].

Understanding disease awareness and referral patterns provides important insights into the management of the patient population receiving evolocumab in this German HEYMANS cohort. These factors may explain why some patients had not initiated intensive LLT, including evolocumab, even when local reimbursement criteria would have allowed initiation of a PCSK9 inhibitor. A recent survey among physicians (general practitioners, cardiologists, and internists) and secondary prevention patients in Germany found that one-third of patients had never been prescribed a change

to their initial LLT dose, irrespective of whether they had achieved a reduction in LDL-C with their prescribed regimen or not [11]. In this survey, only 19% of physicians reported to follow the ESC/EAS recommendations in their entirety, i.e., aim for a ≥ 50% reduction in LDL-C from baseline AND the attainment of LDL-C < 55 mg/dL goal; 65% aimed for the LDL-C goal alone and 28% aimed for the 50% LDL-C reduction (multiple responses were possible; personal communication O. Weingärtner). Only about a third of patients knew their current LDL-C level and 40% were aware of their recommended LDL-C goal. The authors concluded that there was insufficient implementation of the ESC/EAS guidelines in Germany regarding therapeutic escalation strategies and a lack of specialist involvement [11].

As set out by the German reimbursement regulations, the initial prescription of PCSK9 inhibitors must be done by specialists in cardiology, nephrology, endocrinology and diabetology, and angiology or by dedicated lipid clinics. General practitioners or other healthcare professionals should refer patients requiring more intensive lipid management to the specified specialties [5]. The importance of combined LLT has been consistently observed in clinical practice [7, 16], including in the present HEYMANS Germany cohort, where attainment of LDL-C < 55 mg/dL was higher in patients receiving evolocumab in combination with statin and/or ezetimibe (69%) than in those who did not receive background LLT (49%). It was observed that along with the initiation of evolocumab, patients' background LLT regimen was also adapted in some patients. The proportion of patients with statins and/or ezetimibe increased from 31% to 37% and the proportion of those receiving ezetimibe alone increased from 10% to 14%, reducing the proportion of patients without any background LLT by 10%. The most recent iteration of the German reimbursement regulation classifies the use of bempedoic acid as an option to consider before PCSK9 inhibitor [15]. In patients who cannot tolerate intensive statin therapy and were previously receiving PCSK9 inhibitor monotherapy to adequately lower LDL-C, additional options for treatment intensification could now include low dose statins, ezetimibe, bempedoic acid, or a combination of bempedoic acid and ezetimibe.

Persistence with evolocumab therapy at 12 months was high (91%) and remained similarly high in the long term among patients who entered the extension phase of the study (94% at 30 months), in line with the overall HEYMANS analysis (93% at 12 months and 92% at 30 months) [17]. Our findings are generally aligned with those of other evolocumab studies in real-world clinical practice. A persistence of 92% was found in the Canadian ZERBINI study which followed patients for 12 months and allowed a gap between two consecutive administrations of evolocumab of up to 56 days [19]. In the GOULD registry following patients in the USA over 2 years using structured telephone interviews, 92% of patients reported they were still taking evolocumab at 2 years [20]. However, there is currently no standard definition of persistence. Different definitions to the one used in the present study have been reported in the literature, e.g., filled prescriptions [21], non-violation of certain gap windows [19, 22], or self-reported surveys [20, 23]. Additionally different periods of observation have been published [19–23]. Studies of PCSK9 inhibitor persistence are therefore not readily comparable.

The present study did not show any new safety signal associated with evolocumab use. Of a total of 8% of patients reporting any treatment-emergent adverse drug reactions, the most frequent were musculoskeletal and connective tissue disorders (3%), other events occurred in ≤ 1% of patients. A recent meta-analysis evaluating the safety and tolerability of PCSK9 inhibitors (evolocumab and alirocumab) showed that they are not associated with an increased risk of adverse events or toxicity in addition to that observed with background LLT [24].

This study has some limitations. Any observational study has a risk of selection bias towards either patients with good response to the study drug or towards patients most in need of the study drug. To avoid enrollment bias via selective invitation of a particular patient profile to participate in the study, the study

protocol defined that at the site level, all eligible patients were required to be invited to enroll in chronological order of attending the clinic, until the local enrollment cap had been reached. Persistence data may be slightly overestimated because of the following considerations: Almost half of the patients (170/380) were receiving evolocumab for > 6 months prior to study enrollment. It is possible that long-term users of evolocumab may be more likely to persist with their established treatment routine than those who started more recently. In Germany, evolocumab initiation and treatment monitoring need to be conducted by experts or dedicated lipid clinics. Regular checkups through experts with high disease awareness can encourage persistence with treatment. In the setting of an observational study, regular monitoring and structured documentation of drug use may introduce a study effect overestimating persistence. Nevertheless, as stated, our results are consistent with previous studies on evolocumab persistence [19, 20]. The study period spanned the periods of validity of the 2016 ESC/EAS guidelines [10] and the subsequent 2019 iteration which was published on 31 August 2019 [5]. Patients in Germany had a median (Q1, Q3) duration of evolocumab exposure of 12 (12, 18) months during the study's overlap with the 2016 guideline period. This is mostly aligned with the total duration of evolocumab exposure, which was 12 (12, 30) months. Therefore, most patients were treated to attain the LDL-C goal of < 70 mg/dL [10] while on study (73% attainment), overestimating the goal attainment reported here using the < 55 mg/dL goal [5] (59% attainment). The study partly coincided with the COVID-19 pandemic which started in February 2020. However, only 134 out of a total of 2478 LDL-C measurements were conducted during the pandemic period (from 01 March 2020 to end of study). It is therefore expected that less frequent patient monitoring during the COVID-19 pandemic (2.76 LDL-C measurements per patient-year versus 4.39) did not substantially alter the treatment outcomes.

CONCLUSIONS

Data from the German HEYMANS cohort corroborate previous reports on evolocumab effectiveness and safety in clinical practice. In Germany, evolocumab initiation was associated with a rapid and sustained reduction in LDL-C and persistence with evolocumab treatment was high. The importance of using highly intensive combination therapy was confirmed as LDL-C goal attainment was higher in patients receiving evolocumab in combination with statins and/or ezetimibe compared with those who were receiving evolocumab alone. Patients tolerated evolocumab well, also when used in the long term, corroborating evidence that addition of PCSK9 inhibitors to statins and/or ezetimibe is not associated with an increased risk of adverse events or toxicity. There seems to be a discordance between physicians' judgement of LDL-C goal fulfillment found in recent surveys and the treatment reality.

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study investigators for the German study cohort and acquired the data. Ian Bridges conducted statistical analysis of the data. All authors substantially contributed to the interpretation of the study results. Uwe Fraass and Anja Tabbert-Zitzler were responsible for study oversight in Germany and interpreted the data in the context of Germany clinical practice. All authors were involved in drafting of the manuscript, provided critical revisions for important intellectual content, approved the final version submitted for publication, and agreed to be accountable for all aspects of the work.

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Data Availability. Qualified researchers may request data from Amgen clinical studies. Complete details are available at https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/.

Declarations

Conflict of Interest. Michael Lehrke received grants and personal fees from Boehringer Ingelheim, MSD, Novo Nordisk and personal fees from Amgen, Sanofi, AstraZeneca, Bayer, Lilly, Daiichi Sankyo, Novarits. Volker Schettler declares to have received speaker's fees, travel support and/or study grants from Amgen GmbH, Akcea GmbH, B.Braun Avitum AG, Daiichi Sankyo Deutschland GmbH, Fresenius Medical Care AG & Co. KGaA, KWHC Health Consulting GmbH, Novartis Pharma GmbH, Novo Nordisk GmbH, Sanofi-Aventis GmbH, Vifor Deutschland GmbH. Matthias Girndt declares speaker's and advisory fees from Amgen GmbH, Astellas GmbH, Bayer Vital GmbH, Daiichi Sankyo GmbH, Hexal AG, Novartis GmbH, Novo Nordisk GmbH, Pfizer GmbH, Sanofi GmbH, Vifor Fresenius GmbH. Anja Vogt declares speaker's and advisory fees from Aegerion, Amgen GmbH, Daiichi Sankyo GmbH, MSD GmbH, Novartis GmbH, Sanofi GmbH. Kausik K. Ray reports grants/personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cargene, Daiichi Sankyo, Esperion, Kowa, Lilly, New Amsterdam Pharma, Novartis, Pfizer, Sanofi-Regeneron, Silence Therapeutics and Scribe Therapeutics. Ian Bridges is an employee of Amgen Ltd and stockholder of Amgen; Uwe Fraass and Anja Tabbert-Zitzler are employees of Amgen GmbH and stockholders of Amgen; Nafeesa N. Dhalwani is an employee of Amgen Inc. and stockholder of Amgen.

Ethical Approval. This study was conducted according to the Declaration of Helsinki and the guidelines of the International Council for Harmonization. The study was registered in ClinicalTrials.gov (Identifier NCT02770131). The study protocol and the protocol amendments were approved by the institutional ethics committees of each participating study center (Supplemental Table S1); the ethics committee of the Bavarian state medical association acted as the lead ethics committee for the German sub-study of HEYMANS (study reference number 16030). All patients or their legally acceptable representatives provided written informed consent before participation in this study.

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