

Evolocumab use in clinical practice in Switzerland: final data of the observational HEYMANS cohort study

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Abstract

Aims: The HEYMANS study observed patients receiving evolocumab as part of routine clinical hyperlipidemia management. It was designed to capture data on clinical parameters relevant to health authorities and physicians.

Methods: This was a European multi-country observational cohort serial chart review study; data on the Swiss cohort are reported here. Patients were prescribed evolocumab as per the Swiss reimbursement criteria in force at the time and were invited chronologically. The study consisted of a 6-month period prior to initiation of evolocumab, a 12-month core observation period (entered by 75 patients, completed by 74 patients), and an 18-month extended observation period (entered by 40 patients, completed by 34 patients). The primary objective was to describe the clinical characteristics of patients receiving evolocumab. Secondary objectives included to describe lipid levels, evolocumab use, and patterns of use of other lipid-lowering therapies (LLT, that is, statins and/or ezetimibe) over time. The study was conducted in the Swiss cohort between May 2017 and June 2021.

Results: Patients who received evolocumab in Swiss routine practice mostly were in secondary prevention (93%) and had a history of statin intolerance (85%) with 53% receiving no background LLT. One-third had familial hypercholesterolemia. Patients initiated evolocumab at a median low-density lipoprotein cholesterol (LDL-C) of 3.6 mmol/L, which decreased by 54% within 3 months to 1.6 mmol/L and was stable thereafter. Overall, 61% achieved the LDL-C goal of <1.4 mmol/L with more patients attaining this goal when they received evolocumab with a statin and/or ezetimibe (84%) compared to 41% when receiving evolocumab alone. An LDL-C reduction of ≥50% was achieved by 85% of patients. Persistence with evolocumab at 12 months was 85%.

Conclusion: In Swiss clinical practice, evolocumab was mainly prescribed to patients with very high cardiovascular risk, who had very high LDL-C levels. Most patients continued to use evolocumab throughout the study period. In these patients, LDL-C was reduced by >50% within 3 months and LDL-C reductions were maintained over time. Guideline-recommended LDL-C goals for this very high-risk cohort were more frequently attained in patients receiving a combination of statin and/or ezetimibe and evolocumab.

Trial registration: ClinicalTrials.gov Identifier: NCT02770131.

Keywords: cardiovascular risk, evolocumab, guidelines, LDL-C, PCSK9i, registry

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Introduction

In Switzerland, cardiovascular diseases were responsible for >107,000 hospitalizations and >20,500 deaths in 2020, making them the leading cause of death [representing almost one-third

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(27%) of all deaths in Switzerland].¹ The retention of low-density lipoprotein cholesterol (LDL-C) and other cholesterol-rich apolipoprotein (Apo) B-containing lipoproteins within the arterial wall was identified as the key initiating event in atherogenesis.² Lipid modification is thus an essential way of reducing cardiovascular risk.

The Swiss Atherosclerosis Association (AGLA)³ follows the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) dyslipidemia guidelines⁴ and the 2021 ESC guidelines on cardiovascular disease prevention.⁵ These guidelines recommend the use of lipid-lowering therapies (LLT) to achieve a set of LDL-C goals, that is, a $\geq 50\%$ LDL-C reduction from the untreated level (or extrapolated untreated level, if already pre-treated) and the attainment of LDL-C < 1.8 mmol/L in patients with a high or < 1.4 mmol/L in patients with a very high cardiovascular risk. The AGLA, the 2019 ESC/EAS dyslipidemia, and 2021 ESC prevention guidelines recommend the use of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) if the LDL-C goals are not achieved at maximally tolerated statin doses $\pm$ ezetimibe.³⁻⁵ The 2022 iteration of the Swiss reimbursement regulations mandate that prescription of a PCSK9i can only be continued, if an LDL-C reduction of $\geq 40\%$ compared with the baseline value is achieved under the maximally intensified LLT or when an LDL-C value lower than 1.4 mmol/L has been reached within 6 months of treatment initiation.⁶

Numerous studies have demonstrated the difficulty of attaining the guideline-recommended goals, especially when patients do not receive high-intensity statins $\pm$ ezetimibe or a combination with a PCSK9i.⁷⁻⁹ The recent cross-sectional DA VINCI study investigated LDL-C goal attainment in primary and secondary care across 18 European countries and found that only 33% of patients achieved their risk-based 2019 ESC/EAS LDL-C goal. In the DA VINCI study, a strategy of combining PCSK9i plus background statin $\pm$ ezetimibe was found to increase LDL-C goal attainment, compared with PCSK9i alone.⁸

Studies investigating attainment of the then current 2016 ESC/EAS guideline¹⁰ recommended LDL-C goals (< 2.6 mmol/L for high risk and < 1.8 mmol/L for very high-risk patients) found that in Switzerland, less than 40% of patients

with acute coronary syndromes achieved these goals.^{7,11,12} In peripheral artery disease, attainment of LDL-C < 1.8 mmol/L was 45% in 2017.¹³ If these results are extrapolated to the presently valid 2019 ESC/EAS guideline LDL-C targets,⁴ the goal achievement rate would be even lower. The Explore Clinical Utility of Evolocumab in Combination with an e-Health System: Swiss Prospective Observational Study in Patients with clinical Atherosclerotic Cardiovascular Disease (ECARA) study was conducted between 2017 and 2019, when PCSK9i were already available. It showed that the then current LDL-C goal of < 1.8 mmol/L was achieved by most patients (74% of previously PCSK9i naïve and 88% of PCSK9i pre-treated patients), especially when the PCSK9 monoclonal antibody evolocumab was given in combination with a statin $\pm$ ezetimibe (79% and 91%, respectively). When results were extrapolated to the current LDL-C target of < 1.4 mmol/L, patients receiving combination therapy were substantially more successful in attaining this goal (PCSK9i naïve patients: 74% of those with background LLT *versus* 63% without background LLT; PCSK9i pre-treated patients: 80% of those with background LLT *versus* 53% without background LLT). In ECARA, 89% of patients reported full adherence to the evolocumab administration schedule and 97% continued evolocumab therapy over 12 months.¹⁴

The ‘cHaractEristics of hYperlipidaemia pAtieNts at initiation of evolocumab and treatment patternS’ (HEYMANS) study describes clinical characteristics and LDL-C control among patients initiating evolocumab treatment in 12 European countries.^{15,16} Final data from the Swiss HEYMANS cohort are reported here to strengthen the available evidence from Switzerland (ECARA)¹⁴ with additional patients and an increased duration of treatment to up to 30 months.

Materials and methods

Study design and patient population

The European multi-country HEYMANS observational cohort serial chart review study (ClinicalTrials.gov Identifier: NCT02770131) included patients receiving evolocumab as per local reimbursement rules in force at the time of enrolment (Supplemental Table S1).^{6,15} Site invitation was based on interest in participation,

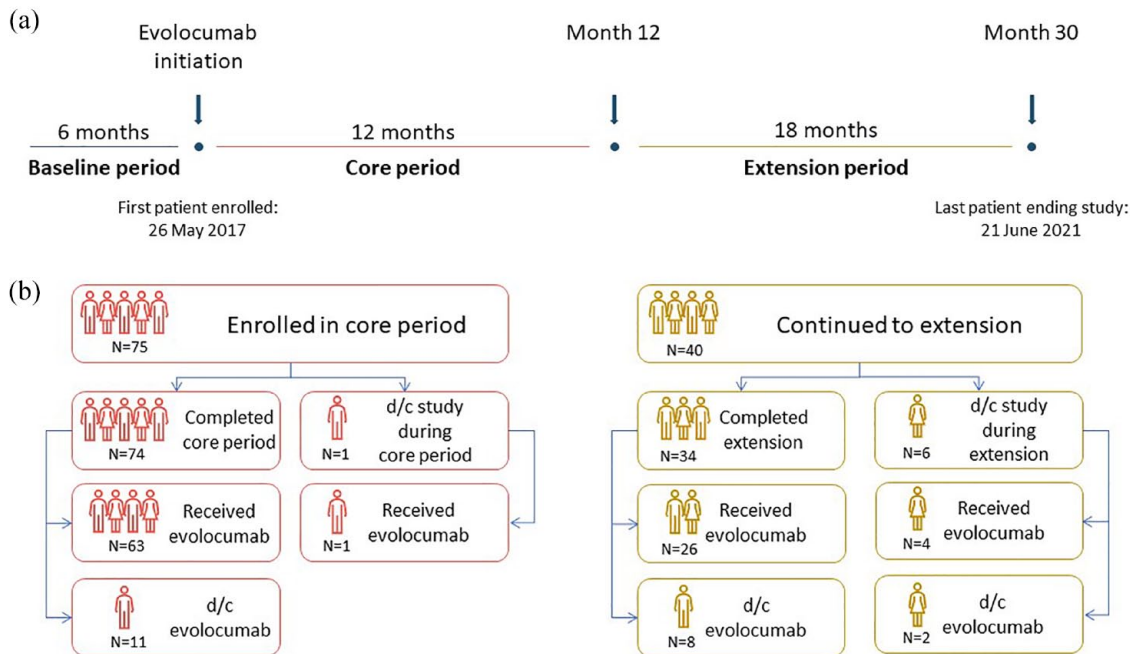


Figure 1. Study schema and patient disposition. (a) Study schema and (b) patient disposition. All 75 patients were enrolled only after initiation of evolocumab at physician discretion, independent of the study protocol. d/c, discontinued.

willingness and ability to comply with the protocol and data entry conventions, and agreement to follow the subjects throughout the observation period. At the site level, all eligible patients were invited to enroll in chronological order of attending the clinic, until the local enrolment cap had been reached. The sample size was determined to enable precise estimates of the primary and secondary outcome measures for the overall HEYMANS study and each of the 12 participating countries and aimed for an average of 130 patients per country.

The study followed patients retrospectively and/or prospectively from evolocumab initiation (baseline). Data were collected through serial review of patients' charts. The core observation period spanned from 6 months before to 12 months after initiation of evolocumab [Figure 1(a)]. The core period included consenting patients ≥ 18 years of age who initiated evolocumab from 1 August 2015 onwards (as defined in the study protocol for the overall cohort) as part of their routine dyslipidemia management as per Swiss reimbursement criteria (ethics committee approval for Switzerland was on 4 April 2017). Patients who were enrolled in an interventional

study of PCSK9i within 12 weeks prior to initiation of evolocumab or patients who received a PCSK9i in routine practice were excluded from the study.

An extension period from month 13 onwards to a maximum of 30 months post-evolocumab initiation [Figure 1(a)] was defined in a protocol amendment (in February 2018) and included only those patients still on study at the time of ethics committee approval of the amendment. The Swiss cohort enrolled the first patients in May 2017 and the last patient ended the study in June 2021; five study centers were involved (University Hospital Basel, Cardiac Center Ticino, Municipal Hospital Triemli-Zurich, University Hospital Geneva, University Hospital Zurich). Patients followed their routine schedule of visits, and no study-specific visits were required; measurement of laboratory variables (e.g. LDL-C) was thus infrequent, especially during the extension phase.

Outcome measures

The primary study objective was to describe the clinical characteristics of patients at initiation of

evolocumab. For the primary outcome measure, information bias was not anticipated to be applicable, as investigators were aware of the patients' age and sex and paid particular attention to their cardiovascular history as they have been referred for a cardiovascular cause. The secondary objective was to describe parameters associated with the clinical management of hyperlipidemia in patients initiated on evolocumab treatment, such as lipid values, evolocumab use, and use of LLT over time.

Demographics and clinical characteristics, LLT, and lipid profiles were collected from medical records. Comorbidities were defined using national criteria that primarily followed the 2016 ESC/EAS dyslipidemia guidelines.¹⁰ Statin intolerance was determined at the discretion of the treating physician in accordance with local reimbursement criteria.^{17,18} LDL-C measurements were collected as per clinical practice but were summarized in 3-month windows. Evolocumab and LLT use were summarized at the end of each 3-month period. LDL-C goal attainment as per the 2019 ESC/EAS guidelines was defined as reaching an LDL-C value of <1.4 mmol/L (very high-risk patients) or <1.8 mmol/L (high-risk patients) at least once during the follow-up period. Risk levels were defined as per the 2019 ESC/EAS guidelines.⁴

An analysis of evolocumab persistence was conducted based on investigator-documented evolocumab use. Evolocumab persistence was analyzed separately for the core period and the extension: 0–12 months and 13–30 months. Persistence was defined as the proportion of patients who continued to receive evolocumab and remained in the study at specified time points. Evolocumab discontinuation was defined as permanently stopping therapy during the observation period. Patients who stopped the study before the end of month 12 or month 30 but who were still receiving evolocumab were excluded from the persistence analysis.

No formal analysis of safety data was planned, and adverse drug reactions (ADRs) were summarized as reported.

Statistical analysis

This study was descriptive in nature and no hypothesis was tested. Categorical data are displayed as

frequency, percentage with – where appropriate – 95% confidence interval (CI). Continuous data are shown as means with standard deviation (SD) or median with first and third quartile (Q1, Q3). Missing data were not imputed. Attainment of LDL-C goals [<1.4 mmol/L (very high-risk patients) or <1.8 mmol/L (high-risk patients)] was assessed for patients who had at least one post-baseline LDL-C value and were classified as high or very high risk according to the 2019 ESC/EAS guidelines. The percentage of patients achieving a $\geq 50\%$ LDL-C reduction from baseline (ESC/EAS and AGLA guidelines) or a $\geq 40\%$ (Swiss reimbursement regulations), were calculated for all patients who had a baseline and at least one post-baseline LDL-C measurement.

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Ethical considerations

This study was conducted according to the Declaration of Helsinki and was consistent with the guidelines of the International Council for Harmonization. The study protocol was reviewed by the independent lead ethics committee 'Commission cantonale d'éthique de la recherche', Geneva, Switzerland (BASEC ID: 2016-02099) and the local hospital ethics committees in each participating center (Supplemental Table S2). Written informed consent was obtained from each participating patient or their legally appointed representative.

Results

Patient population

Seventy-five patients were enrolled from Switzerland, and 40 patients continued to the extension phase [Figure 1(b); Supplemental Figure S1]. The mean (SD) age at baseline was 59.3 (10.6) years and most patients were male (72%). Almost all patients (93%) were in secondary prevention and 33% had been diagnosed with familial hypercholesterolemia (FH). A history of intolerance to any statin was documented in 85% of patients. Reported cardiovascular risk factors were a history of smoking (60%), hypertension (49%), diabetes mellitus type 2 (7%), and chronic kidney disease (5%). Nearly all patients (97%) had very high cardiovascular risk (Table 1).

Table 1. Baseline characteristics of patients initiating evolocumab ($n=75$).

Baseline characteristic	All patients (N=75)
Male sex, n (%)	54 (72)
Age (years), mean (SD)	59.3 (10.6)
Primary prevention, n (%)	5 (7)
FH without ASCVD	3 (4)
Neither ASCVD nor FH	2 (3)
Secondary prevention, n (%)	70 (93)
ASCVD with FH	22 (29)
ASCVD without FH	48 (64)
FH, n (%)	25 (33)
High cardiovascular risk, n (%)	2 (3)
Very high cardiovascular risk, n (%)	73 (97)
Type 2 diabetes, n (%)	5 (7)
Hypertension, n (%)	37 (49)
Chronic kidney disease, n (%)	4 (5)
Prior/current smokers, n (%)	45 (60)
History of intolerance to any statin, n (%)	64 (85)
Background LLT, n (%)	
None	40 (53)
Statin $\pm$ ezetimibe	27 (36)
Statin with ezetimibe	14 (19)
Statin without ezetimibe	13 (17)
Ezetimibe without statin	8 (11)
ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LLT, lipid-lowering therapy; SD, standard deviation.	

Evolocumab use over time

At baseline, most patients (96%, $n=72$) received evolocumab at a dose of 140 mg once every 2 weeks; 1% ($n=1$) received 420 mg once monthly and 3% ($n=2$) received evolocumab 140 mg once monthly. Persistence with evolocumab treatment at month 12 was 85% ($n=63$

of 74 patients with known evolocumab status; Supplemental Figure S2).

Over the entire 30-months study period, 13 patients (17%) permanently discontinued evolocumab: 7 (9%) on patient request, 3 (4%) due to ADRs, and 1 (1%) each due to requirement for an alternative therapy, reimbursement, and death.

Background LLT over time

At baseline, 53% of patients ($n=40$) were receiving no background LLT, that is, no statins or ezetimibe; 36% ($n=27$) received a statin, with or without ezetimibe and 11% of patients ($n=8$) received ezetimibe alone. Of the patients receiving a statin alone ($n=13$), 54% ($n=7/13$) received a high-intensity statin and 46% ($n=6/13$) received a moderate-intensity statin. Of the patients receiving a statin in combination with ezetimibe ($n=14$), 79% ($n=11/14$) received high-intensity statin and 21% ($n=3/14$) received moderate-intensity statin. LLT usage patterns did not substantially change during the core period (Supplemental Figure S3).

LDL-C levels over time

Overall, patients had a median (Q1, Q3) baseline LDL-C value of 3.6 (3.0, 4.5) mmol/L. Within the first 3 months of evolocumab treatment, median (Q1, Q3) LDL-C levels were reduced by 54% (−67%, −44%) to a median of 1.6 (1.2, 2.2) mmol/L. Similar levels of reduction were maintained over the 30-month study period (Figure 2).

LDL-C goal attainment

Sixty-one percent of patients ($n=42$) attained the LDL-C goal of <1.4 mmol/L at least once during follow-up. LDL-C goal attainment was higher in patients receiving evolocumab with background LLT (84%, $n=27$) than in those receiving evolocumab without background LLT (41%, $n=15$; Figure 3). Of the patients with atherosclerotic cardiovascular disease (ASCVD) and FH ($n=22$), 67% ($n=12$) attained the LDL-C goal of <1.4 mmol/L and 64% ($n=30$) of patients with ASCVD without FH ($n=48$) attained this goal (Supplemental Figure S4). Eighty-five percent of patients

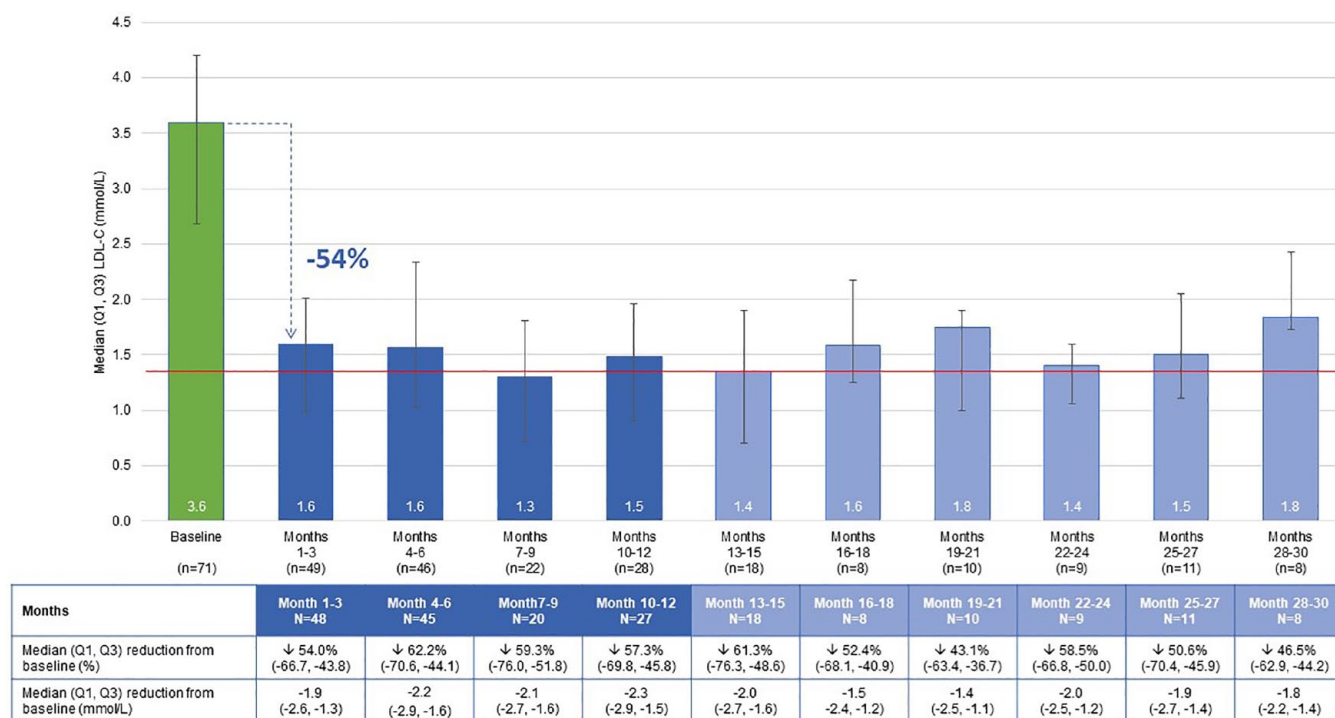


Figure 2. LDL-C levels over time.

The red line represents an LDL-C level of 1.4 mmol/L. LDL-C, low-density lipoprotein cholesterol; Q, quartile.

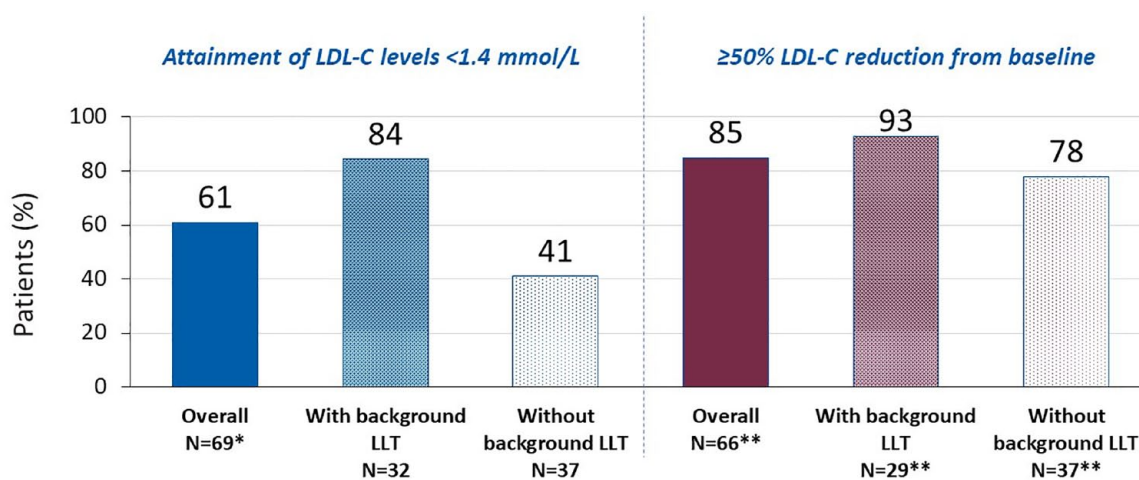


Figure 3. Attainment of ESC/EAS-recommended LDL-C goals.

The 2019 ESC/EAS guidelines recommend an LDL-C goal of <1.4 mmol/L for patients with very high cardiovascular risk. In the Swiss cohort, 2 patients had high and 73 patients had very high cardiovascular risk. The ESC/EAS guidelines recommend an LDL-C reduction of ≥50%. *LDL-C goal attainment could be assessed for the 69 patients who had at least one post-baseline LDL-C measurement; **66 patients had a baseline and at least one post-baseline LDL-C measurement and could be assessed for percentage LDL-C reduction from baseline. EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

(n=56) achieved a ≥50% LDL-C reduction and 92% (n=61) achieved a ≥40% LDL-C reduction from baseline at least once during follow-up.

Summary of safety findings

Overall, 13% of patients (n=10) reported ADRs; none were serious or fatal. Supplemental Table S3 summarizes ADRs.

Discussion

We aimed to describe the characteristics of patients at initiation of evolocumab in routine clinical practice in Switzerland and to estimate parameters associated with the clinical management of hyperlipidemia, such as lipid values, evolocumab use, and use of LLT over time. As can be expected from the Swiss reimbursement criteria at the time, we found that evolocumab was mainly prescribed to patients with very high cardiovascular risk and very high LDL-C levels. LDL-C levels improved rapidly, and reductions were maintained over time as evolocumab was persistently used in the long-term. LDL-C goals for this very high-risk cohort were more frequently attained in patients receiving a combination of evolocumab and statin and/or ezetimibe.

The HEYMANS study is the first to report data on long-term evolocumab use in real-world practice in 12 countries in Europe, including routine Swiss clinical practice, providing data for up to 30 months of therapy; the previously published Swiss ECARA study only observed patients for 12 months.¹⁴ The randomized, placebo-controlled FOURIER trial offered an open-label extension (OLE) period with a maximum evolocumab exposure in the parent plus OLE periods of 8.4 years.¹⁹ In addition, the OSLER-1 open-label extension study²⁰ as well long-term data from patients with FH²¹ have reported on the long-term effectiveness of evolocumab in very high-risk patients.

HEYMANS confirms the effectiveness of evolocumab in reducing LDL-C levels rapidly and substantially (−54% within the first 3 months in Swiss patients); this reduction was maintained over time for up to 30 months (Figure 2). Similar reductions have been consistently observed across all countries participating in HEYMANS, despite widely differing reimbursement environments, and thus different populations eligible for evolocumab use.^{15,16}

Long-term persistence with evolocumab was high with 85% at month 12 (Supplemental Figure S2). The most frequent reason for discontinuation was a patient request. With only 13 patients permanently discontinuing evolocumab over the entire study period, a detailed analysis of their patient characteristics and background LLT use was not meaningful. However, in the overall HEYMANS

study population, the clinical characteristic of the patients who discontinued evolocumab (8%, $n=164/1951$) were generally similar to the Swiss cohort and more than 50% of patients who discontinued evolocumab were not receiving a statin or ezetimibe at discontinuation. In the overall cohort, evolocumab persistence at 12 months was 93% and at 30 months it was 92%.¹⁶ In ECARA, 89% of patients reported adherence to the planned evolocumab administration schedule, that is, reported no missed doses during the 12 months of observation.¹⁴ Although the definitions of persistence in HEYMANS and adherence in ECARA differed, these results suggest that patients are comfortable with using evolocumab in the long-term.

The DA VINCI study suggested that statins at maximally tolerated dose, combined with ezetimibe and a PCSK9i, allowed more patients to attain LDL-C goals than any regimen containing lower-intensity statins and/or fewer treatment components,⁸ a trend which was also seen in the overall HEYMANS cohort.¹⁵ In Switzerland, over 60% of patients achieved LDL-C <1.4 mmol/L and 85% achieved a ≥50% reduction in LDL-C. Attainment of these goals was higher when evolocumab was used in combination with a statin ± ezetimibe (84% for LDL-C <1.4 mmol/L and 93% for ≥50% LDL-C reduction) than with evolocumab alone (41% and 78%, respectively; Figure 3).

Patient characteristics and their underlying condition impact treatment outcomes. The Swiss HEYMANS cohort was a population of patients with very high cardiovascular risk; only two patients were classified as high cardiovascular risk. Accordingly, patients were mostly (93%) treated in the secondary prevention setting, that is, they already had established ASCVD. For the overall HEYMANS cohort, different groups of patients were analyzed to better understand the impact of reimbursement restrictions in certain populations: those with ASCVD without FH, those with ASCVD with FH, those with FH without ASCVD, and those with neither FH nor ASCVD. It was found that in very high-risk populations with established ASCVD, attainment of the <1.4 mmol/L LDL-C goal was similar in patients with or without FH.¹⁵ This was also observed in the Swiss HEYMANS cohort (Supplemental Figure S4). In the overall

HEYMANS primary prevention cohort (FH without ASCVD), goal attainment was much higher in high-risk patients (LDL-C goal of $<1.8\text{ mmol/L}$) than in very high-risk patients (LDL-C goal of $<1.4\text{ mmol/L}$).¹⁵ The number of primary prevention patients was too low in the Swiss cohort for meaningful interpretation.

There is a correlation between the LDL-C level at baseline and goal attainment, at least at the beginning of treatment. In the overall HEYMANS cohort, it was shown that lower LDL-C levels were attained after 3 months of evolocumab treatment in those countries where patients had lower LDL-C levels at baseline.¹⁵ However, the reimbursement thresholds for LDL-C at which PCSK9i could be prescribed were consistently higher across all countries participating in HEYMANS than the 2019 ESC/EAS guideline-recommended LDL-C thresholds for PCSK9i use. Additionally, in many countries the actual baseline LDL-C levels at evolocumab initiation were higher than the relevant LDL-C reimbursement threshold. Overall, patients enrolled in HEYMANS had a baseline LDL-C level three times higher than the 2019 ESC/EAS guideline-recommended threshold for PCSK9i initiation;¹⁵ this was also the case in Switzerland. Although evolocumab was shown to quickly lower LDL-C and maintain the reduced LDL-C level over time, the FOURIER-OLE study¹⁹ demonstrated the importance of early treatment initiation. After the placebo-controlled parent period, patients receiving placebo were allowed to cross over to evolocumab for the OLE period. It was found that although initial placebo patients attained a similar LDL-C level after crossing to evolocumab, the earlier initiation of intensive LDL-C lowering therapy in the initial evolocumab group was associated with continued accrual of cardiovascular benefit over the subsequent years.¹⁹

In the earlier period of the current study (in 2017 and 2018), patients with established ASCVD were permitted to receive PCSK9i when their LDL-C level was $>3.5\text{ mmol/L}$ (or 2.6 mmol/L for those with rapid progression). The reimbursement criteria were updated in 2019 to allow PCSK9i to be prescribed to very high cardiovascular risk patients with a clinically manifest atherosclerotic ischemic CV event with LDL-C $>2.6\text{ mmol/L}$ after maximally tolerated doses of statins $\pm$ ezetimibe, or treatment with ezetimibe

only if statin intolerant; this may have affected the management of patients who enrolled in HEYMANS after the update. However, in the present analysis, patients in the Swiss cohort were enrolled with a median LDL-C level of 3.6 mmol/L , in line with the version of the PCSK9i reimbursement regulations that was valid before the 2019 update. It is worth contrasting these criteria with other countries from HEYMANS where the reimbursement criteria do not include a threshold of LDL-C, where the proportion of statin intolerant patients is lower than the 85% seen in the Swiss cohort. This suggests that use of evolocumab is dictated by reimbursement threshold *versus* clinical need.

This study has some limitations. In the Swiss cohort, only a very small number of patients participated in the extension phase of this study. Therefore, outcomes from month 13 to month 30 need to be interpreted with caution. Persistence data may be slightly overestimated due to the following considerations: Twenty-six patients were receiving evolocumab for >6 months prior to study enrolment; long-term users may have been more likely to persist with evolocumab than those who had a shorter treatment routine. Additionally, prescription of evolocumab and follow-up checks in Switzerland are required to be conducted by dedicated experts (<http://www.bag.admin.ch/sl-ref>) who can encourage persistence with treatment. Nevertheless, our results are similar to those of previous studies on evolocumab persistence.^{22,23} The study partly coincided with the COVID-19 pandemic, which started in February 2020. However only 22 LDL-C measurements in total were conducted during the pandemic period (1 March 2020 to end of study), while 273 LDL-C measurements were carried out during the pre-pandemic period (first evolocumab administration to 29 February 2020). It is therefore expected that the impact of the COVID-19 pandemic was small. Nevertheless, it was observed that the number of LDL-C measurements per patient-year fell from 2.45 in the pre-pandemic period to 1.12 in the COVID-19 period. Persistence with evolocumab at 30 months was not reported because of the very low number of patients participating in the extension phase. It needs to be noted that there is currently no standard definition of persistence and so different definitions, as well as different periods of observation, are used in studies of persistence with other medications.

Conclusion

In Swiss clinical practice, evolocumab use was associated with a rapid, clinically relevant LDL-C reduction of more than 50%, which was maintained for up to 30 months. Long-term persistence to evolocumab treatment in clinical practice was high. Over 60% of patients achieved LDL-C <1.4 mmol/L and 85% achieved a $\geq 50\%$ reduction in LDL-C. When evolocumab was used in combination with a statin $\pm$ ezetimibe, LDL-C goal attainment in Switzerland was as high as 84%. Therefore, reimbursement criteria should enable patients to receive the optimal therapy to improve patient health. Especially, secondary prevention patients with very high cardiovascular risk should be treated with a PCSK9i in combination with the highest tolerated statin intensity $\pm$ ezetimibe. General practitioners should make sure to refer patients to the specialist for adequate treatment.

Declarations

Ethics approval and consent to participate

This study was conducted according to the Declaration of Helsinki and was consistent with the guidelines of the International Council for Harmonization. The study protocol was reviewed by the independent lead ethics committee 'Commission cantonale d'éthique de la recherche', Geneva, Switzerland (BASEC ID: 2016-02099) and the local hospital ethics committees in each participating center (Supplemental Table S2). Written informed consent was obtained from each participating patient or their legally appointed representative.

Consent for publication

Not applicable.

Author contributions

Isabella Sudano: Investigation; Writing – review & editing.

Stephan Krähenbühl: Investigation; Writing – review & editing.

François Mach: Investigation; Writing – review & editing.

Anne Anstett: Conceptualization; Writing – original draft.

Nafeesa Dhalwani: Conceptualization; Writing – review & editing.

Ian Bridges: Formal analysis; Writing – review & editing.

Mahendra Sibartie: Conceptualization; Writing – review & editing.

Kausik K. Ray: Conceptualization; Writing – review & editing.

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Competing interests

IS reports grants from Amgen during the conduct of the study, and grants and personal fees from Amgen, AstraZeneca, Daiichi Sankyo, Medtronic, MSD, Recordati, Sanofi, and Servier, outside the submitted work. SK was the local principal investigator of the FOURIER trial. IB, MS, AA, and ND are Amgen employees of and hold stock in Amgen. FM declares no conflict of interest. KKR reports grants from Amgen during the conduct of the study, and 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 Zuellig Pharma, and grants and personal fees from Amgen, Daiichi Sankyo, MSD, Sanofi-Regeneron, and Pfizer, outside the submitted work.

Availability of data and materials

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

Supplemental material

Supplemental material for this article is available online.

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