Original Research

The First Report of a Real-world Experience With a PCSK9 Inhibitor in a Large Familial Hyperlipidemia and Very-high-risk Middle Eastern Population

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ABSTRACT

Purpose: Evolocumab, a monoclonal inhibitor of proprotein convertase subtilisin/kexin 9, has been shown to reduce proatherogenic lipoproteins in patients with or without familial hypercholesterolemia (FH), diabetes mellitus, or atherosclerotic cardiovascular disease (ASCVD). We explored the safety profile and clinical effectiveness of evolocumab in an outpatient population of Emirati individuals with FH diagnosed per Dutch Lipid Clinic Network criteria, previous ASCVD, or statin intolerance.

Methods: This study was a retrospective review of patients initiating evolocumab treatment for any indication at Imperial College London Diabetes Centre between 2017 and 2020. All individuals followed up for at least 90 days or with at least one lipid panel postinitiation were included. Participants were subclassified into primary prevention (no previous ASCVD event, n = 81) and secondary prevention (any prior clinical ASCVD event, n = 102) groups.

Findings: Evolocumab was initiated in 183 individuals (mean [SD] age, 51.5 [12.4] years; 51% male); 108 (59%) had a clinical or genetic FH diagnosis, and 70.5% had diabetes mellitus. Statin intolerance was a treatment indication in 60 (32.8%) individuals. At 90 days, substantial reductions in serum LDL-C, triglycerides (TG), and total cholesterol:HDL-C (TC:HDL-C) were observed in both the primary and secondary prevention groups, and both FH and non-FH individuals. In the primary prevention group, median (interquartile range) reduction in LDL-C was 43.7% (10.8%; 63.0%); TG, 15.0% (7.2%; 35.3%); and TC:HDL-C, 31.5% (11.1%; 46.0%). In the secondary prevention group, median (interquartile range) reduction in LDL-C was 48.3% (22%; 70%); TG, 19.6% (1.2%; 32.5%); and TC:HDL-C, 32.6% (14.6%; 46.3%) (all, $P < 0.0001$). American College of Cardiology/American Heart Association LDL-C targets were consistently achieved in 114 (62.3%) patients during a follow-up of 359 (79-639) days. Nonattainment of the LDL-C target was attributed to nonadherence in 36 (52.2%) patients and discontinuation of treatment in 14 (20.3%) patients. Evolocumab was discontinued in 4 patients because of adverse events.

Implications: This study is the first from the Middle East and North Africa region that reports the real-world efficacy of evolocumab in a mixed risk population of individuals with FH and other non-FH indications. Clinically meaningful and sustained reductions in LDL-C, TG, and cholesterol ratios were observed after evolocumab initiation. Few adverse events were reported in this predominantly Arabic population, consistent with previous safety reports for evolocumab.

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Notable strengths of this study include a relatively large cohort, patient heterogeneity and high retention, and a minimum follow-up of 1 year. Despite these strengths, the study has some limitations, including the selection bias due to the retrospective design and absence of comparative group. (*Clin Ther.* 2022;44:1297–1309.)

Keywords: atherosclerotic cardiovascular disease, diabetes mellitus, evolocumab, familial hypercholesterolemia, LDL-C, PCSK9 inhibitor, real-world experience.

INTRODUCTION

LDL-C is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD). Recent evidence supports intensive LDL-C reduction in patients with ASCVD, but many individuals do not achieve their target LDL-C despite maximal conventional lipid-lowering therapy (LLT).[1,2] This has been attributed to factors such as pharmacogenetic effects on statin response, very high baseline LDL-C concentrations as seen in familial hypercholesterolemia (FH), and lack of adherence to therapies.[3] The proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor family is approved for use in patients with established ASCVD who require intensification of lipid reduction to meet American College of Cardiology/American Heart Association (ACC/AHA)[4] and/or European Society of Cardiology/European Atherosclerosis Society (ESC/EAS)[5] treatment targets for secondary prevention, as well as for the primary prevention of ASCVD in people with inherited hypercholesterolemia (homozygous and heterozygous) and in patients unable to tolerate a statin.[6–10]

In clinical trials, the PCSK9 inhibitor evolocumab as monotherapy reduced LDL-C levels up to 60% in patients with and without FH, diabetes mellitus, and/or ASCVD and was well tolerated.[1,3,11] Current ESC/EAS guidelines estimate LDL-C reductions of up to 85% when PCSK9 inhibitors are used in combination with a statin and ezetimibe.[5] The FOURIER (Further Cardiovascular Outcomes Research With PCSK9i [Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors] in Subjects With Elevated Risk) trials reported reductions in ASCVD events of 15%, with no significant differences in adverse events (AEs) among treatment groups.[2] However, there is little evidence in the literature regarding real-world clinical use of PCSK9 inhibitors, particularly in Arab populations and the Middle East and North Africa (MENA) region. The present study explored the safety profile and clinical effectiveness of evolocumab in a predominantly Emirati outpatient population.

PARTICIPANTS AND METHODS

Participants and Study Design

This study followed an observational retrospective cohort design and was conducted at the Imperial College London Diabetes Centre (ICLDC), Abu Dhabi, United Arab Emirates. ICLDC is an outpatient facility that operates specialist Diabetology, Endocrinology, Cardiology, Nephrology, Ophthalmology, Internal Medicine, and General Practice clinics. Individuals enrolling for treatment at ICLDC are given the option to consent for the use of their anonymized data in clinical research. Anonymized patient data were retrieved from the ICLDC electronic medical record (EMR) covering the time period between January 2017 and October 2020. The study protocol was approved by the Institutional Research Ethics Committee (IREC054). The study included all patients aged between 18 and 85 years who initiated PCSK9 inhibitor treatment at ICLDC and who attended follow-up with repetition of the lipid panel on at least one subsequent occasion. The time frame to each follow-up visit postinitiation of evolocumab was ≤3 months. Median follow-up was 359 (79-639) days. Evolocumab was administered at the licensed doses of 140 mg once every 2 weeks or 420 mg once monthly. The patients' demographic characteristics, anthropometric measures, FH status, diabetes status and type of diabetes, AEs, and cardiovascular disease diagnoses (*International Classification of Diseases, Tenth Revision* [ICD-10] codes: I21–I21.19, I25–125.83, I73.9, Z86.73, and Z95.1) were recorded.

Information on LLTs used to treat each individual before evolocumab initiation was retrieved from the EMR. Overall, 97% of participants were prescribed a statin before evolocumab initiation, 89% used ezetimibe, and 23% were prescribed omega-3 products. The lipid profile before initiation of evolocumab was considered as baseline. Preexisting or first visit ASCVD and/or cardiovascular events were reported

as ASCVD prevalence, and subsequent ASCVD and/or cardiovascular events were reported as incidence. The cohort was subdivided into primary and secondary prevention groups based on the absence or presence of clinical ASCVD events at initiation of evolocumab, as per the ACC/AHA guidelines (2018–2019).[4] Clinical ASCVD includes acute coronary syndrome, those with a history of myocardial infarction, stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease, including aortic aneurysm, all of atherosclerotic origin. All patients with no previous clinical ASCVD event/history were grouped into primary prevention and all patients with clinical ASCVD event/history prior to initiation of evolocumab were grouped into secondary prevention. For patients in the primary prevention group, 10-year ASCVD risk scores were computed before initiation of evolocumab by using pooled cohort equations.[12] In those without a previous ASCVD or FH diagnosis, individuals with absolute 10-year ASCVD risk scores of <5%, 5% to 7.5%, 7.5% to 20%, and >20% were classified as low, borderline, intermediate, and high risk, respectively.[4] Secondary prevention patients, conventionally recognized as high or very high secondary ASCVD risk according to the latest ESC/EAS guidelines,[5] were further stratified by using the ESC SMART score ASCVD risk calculator[13] (scores ≥5% to <10% and ≥10% categorizing patients as high risk and very high risk, respectively). Untreated LDL-C was estimated by dividing the on-treatment LDL-C values by the reciprocal of the expected percentage per the algorithm proposed by Ruel et al[14] to control for the effect of concomitant statin therapy. The estimated likelihood of an underlying diagnosis of FH was calculated by using the Dutch Lipid Clinic Network score (DLCNS) criteria.[15] FH status was considered definitive in individuals with a DLCNS score ≥8 or a genetic diagnosis.

Study Outcome Measures

The primary outcome was defined as attainment of ACC/AHA guidelines–recommended LDL-C targets of ≥30% reduction or LDL-C <2.6 mmol/L in primary prevention or ≥50% reduction or LDL-C <1.8 mmol/L in secondary prevention.[4] Participants were further analyzed using new the LDL-C value of <1.4 mmol/L as recommended in recent ESC/EAS guidelines.[5] The secondary outcome was incidence of new cardiovascular events after evolocumab initiation, expressed as a composite of myocardial infarction, coronary revascularization, stroke, and unstable angina. Safety was assessed according to AEs (injection site reaction, myalgia, worsening of liver enzyme, nausea, and vomiting) recorded in the EMR. Adherence to treatment was assessed by manual review of clinician entries in the EMR and pharmacy records.

The standard of care at ICLDC for follow-up of patients with hyperlipidemia is to perform clinical review and relevant laboratory investigations every 3 months. Prescribing and dispensing of medication in the United Arab Emirates follows a 3-month schedule, and hence individuals who did not collect their prescribed medication during one 3-month cycle were considered to have lapsed treatment. The median follow-up period of the study individuals was 359 (79-639) days; except where indicated, this was the full duration since initiation of therapy at the time of data collection.

Statistical Analysis

Data are expressed as mean (SD) where normally distributed or as median (interquartile range [IQR]) if not. The Wilcoxon signed-rank test was performed to assess change in lipid parameters (LDL-C, TG, and total cholesterol [TC]:HDL-C ratio) following initiation of evolocumab. Where applicable, this test was also performed to assess the significance of differences among baseline and/or postbaseline characteristics in primary and secondary prevention groups. Cox proportional hazards model and Kaplan-Meier curve analysis were performed to measure the hazard ratio and its significance for the secondary outcome measures of the study. Where data were missing, mean values were imputed, amounting to <2% of the data. Statistical analysis was performed by using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) with the *survival, survminer, coin, psych,* and *tidyverse* packages. Significance was assessed at $P < 0.05$ and at 95% of CI. No correction for multiple comparisons was performed.

RESULTS

Patient Characteristics at Initiation of Evolocumab

A total of 183 individuals met inclusion criteria, of whom 81 (44.3%) received evolocumab on a primary prevention setting and 102 (55.7%) were treated

for secondary prevention. Follow-up loss occurred in only 1 patient. Table I presents baseline clinical and laboratory characteristics of the participants. Overall, age at initiation of evolocumab was 51.5 (12.4) years, and 94 (51.4%) participants were male. In 179 cases (97.8%), evolocumab was administered as 140 mg every 2 weeks; in 4 cases (2.2%), the dose was 420 mg once a month. The most frequently recorded indication for evolocumab use was statin intolerance, noted in 60 individuals (32.8%).

At initiation of evolocumab, 6 patients (3.3%) had a history of myocardial infarction (ICD-10 codes: I21, I21.3, I21.4, I21.19, and I25.2), 49 (26.8%) had coronary artery disease (ICD-10 codes: I25.10 and 125.83), 20 (10.9%) had chronic ischemic heart disease (ICD-10 code: I25), and 13 (7.1%) had aortocoronary bypass graft (ICD-10 code: Z95.1). Seven (3.8%) patients reported preexisting peripheral vascular disease (ICD-10 code: I73.9), and two (1.1%) reported previous transient ischemic attack (ICD-10 code: Z86.73).

A total of 108 individuals were diagnosed with definite FH according to DLCN criteria. Details are given in Table II. Genetic confirmation of FH was established in 6 patients (primary prevention, 2 with homozygous FH and 1 with heterozygous FH; secondary prevention, 3 with heterozygous FH). LDL-C values before and after initiation of evolocumab in patients with FH are presented in **Supplemental Table 1** (see the online version at doi:10.1016/j.clinthera.2022.08.005).

Primary Outcome Measure

A total of 121 (66.1%) patients achieved their individualized LDL-C target determined by following the ACC/AHA guidelines (ie, ≥30% reduction or LDL-C <2.6 mmol/L in primary prevention or ≥50% reduction or LDL-C <1.8 mmol/L in secondary prevention) within 90 days of evolocumab initiation; of these, 114 (94.2%) sustained these results at each subsequent visit over an average follow-up period of 359 (280) days. Changes in LDL-C after initiation of evolocumab over a follow-up period ≥366 days are shown in Figure 1.

Figure 2 shows patient study flow according to sustained or nonsustained LDL-C reduction during follow-up. Sixty-nine (37.7%) individuals did not attain target LDL-C at more than one review. Nonattainment of the LDL-C target at follow-up was attributed to nonadherence in 36 (52.2%), discontinuation of treatment in 14 (20.3%), and interruption of funding or drug supply limitations in 11 (15.9%). Fourteen patients discontinued treatment, 4 due to AEs, 4 prior to surgical procedures, 2 due to pregnancy, and 4 due to concerns regarding potential side effects (eg, nausea, vomiting, injection site reaction).

Analysis of Individuals Achieving LDL-C Values <1.4 mmol/L

The target LDL-C <1.4 mmol/L was set by the ESC/EAS guidelines in 93 individuals at the initiation of evolocumab. Of the total, 38 (40.9%) individuals achieved LDL-C <1.4 mmol/L at ≤90 days of initiation of evolocumab; 23 (60.5%) of these individuals sustained these results at each subsequent follow-up visit over an average follow-up period of 304 (280) days. Figure 3 displays the achievement of LDL-C values <1.4 mmol/L in patients with definite FH. Overall, 15.9% (7 of 44) achieved LDL-C values <1.4 mmol/L after 365 days of therapy.

Secondary Outcome Measure

In the primary prevention group (n = 81), 26 (32.1%) and 9 (11.1%) individuals were classified as at intermediate and high risk of ASCVD, respectively. In the secondary prevention group (n = 102), 92 (90.2%) were considered as very high risk and 10 (9.8%) as high risk according to the ESC Smart SCORE. Six (7.4%) of 81 individuals in the primary prevention group and 35 (34.3%) of 102 individuals in the secondary prevention group were diagnosed with a new cardiovascular event following initiation of evolocumab. The hazard of new ASCVD event corrected for age, sex, smoking status, diabetes status, and FH status was 6 times higher in the secondary prevention group than in the primary prevention group (hazard ratio, 5.8; 95% CI, 2.3-14.4; $P < 0.0001$). Moreover, the estimated hazard adjusted for age, sex, smoking status, diabetes status, and FH status for individuals who achieved their ACC/AHA/ESC/EAS LDL-C targets (LDL-C target achievers) versus those who did not achieve these targets (LDL-C target nonachievers) was 0.46 (95% CI, 0.24-0.89; $P < 0.02$). Figure 4 presents the hazard function among LDL-C target achievers versus nonachievers.

Table I. Clinical and laboratory characteristics of patients with hyperlipidemia at initiation of evolocumab therapy according to the presence or absence of previous atherosclerotic cardiovascular disease. Values are presented as number (percentage), mean (SD) or median (interquartile range) unless otherwise indicated.

Characteristics at Initiation of Evolocumab	Primary Prevention (n = 81)	Secondary Prevention (n = 102)
Age, (in years)*	52.2 (12.4)	55.15 (11.4)
Sex		
Male	36 (44.4%)	58 (56.9%)
Female	45 (55.6%)	44 (43.1%)
Body mass index (n = 180)		
• BMI <18.5 kg/m^2	1 (1.2%)	–
• BMI 18.5 to <25 kg/m^2	10 (12.5%)	10 (10%)
• BMI 25 to <30 kg/m^2	28 (35%)	38 (38%)
• BMI ≥30 kg/m^2	41 (51.3%)	52 (52%)
Ever smoked	22 (27.2%)	28 (29.2%)
Diagnosis		
FH (HeFH and HoFH)*	57 (70.4%)	51 (50%)
Mixed dyslipidemia	7 (8.6%)	7 (6.9%)
DM status		
• Type 1	3 (3.7%)	1 (1.0 %)
• Type 2*	49 (60.5%)	76 (74.5%)
• Normoglycemia	29 (35.8%)	25 (24.5%)
HbA_{1c} (DM cases), %*	7.0 (6.2–7.8)	7.8 (6.4–9.0)
Blood pressure, mm Hg		
• SBP*	120 (112–131)	127 (114.0–134.8)
• DBP	72.4 (66–79)	72.7 (65–80)
Renal function and diseases		
• eGFR (mL/min/1.73 m^2), n = 144*	110.1 (92.3–127.4)	96.1 (81.0–114.6)
• Diabetic nephropathy (ICD-10 codes: E10.21, E11.21)	17 (21.0%)	30 (29.4%)
Comorbidities		
• Essential hypertension (ICD-10 code: I10)*	35 (43.2%)	66 (64.7%)
• Pure hypercholesterolemia (ICD-10 code: E78.0)	27 (33.3%)	22 (21.6%)
Family history, n(%)		
• Family history of CVD	18 (22.2%)	17 (16.7%)
• Family history of DM*	23 (28.4%)	15 (14.7%)
Robust LLTs used before clinical decision to initiate PCSK9-i (evolocumab)		
No. of different statins used since diagnosis		
• None	4 (4.9%)	2 (2.0%)
• One	57 (70.4%)	83 (81.4%)
• Two	20 (24.7%)	15 (14.7%)
• Three	–	2 (2.0%)
LLTs used before evolocumab		
• None	1 (1.2%)	–
• One LLT	80 (98.8%)	102 (100%)
• Statin	77 (95.1%)	100 (98%)
• Ezetimibe	68 (83.9%)	94 (92.2%)

(*continued on next page*)

Table I. (*continued*)

Characteristics at Initiation of Evolocumab	Primary Prevention (n = 81)	Secondary Prevention (n = 102)
LLTs used at initiation of evolocumab		
Statin*	48 (59.3%)	75 (73.5%)
Ezetimibe	68 (83.9%)	94 (92.2%)

BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HbA_{1C} = hemoglobin A_{1C}; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; ICD-10 = *International Classification of Diseases, Tenth Revision;* LLT = lipid-lowering therapy; PCSK9 = proprotein convertase subtilisin/kexin 9; SBP = systolic blood pressure.
*The difference is statistically significant ($P < 0.05$; 95% CI).

Table II. Diagnosis of familial hypercholesterolemia (FH) based on Dutch Lipid Clinic Network (DLCN) criteria.

FH Diagnosis*	Primary Prevention Group	Secondary Prevention Group
Definite†	57 (70.4%)	51 (50.0%)
Probable	11 (13.6%)	12 (11.8%)
Possible†	8 (9.9%)	31 (30.4%)
Insufficient information	5 (6.2%)	8 (7.8%)
Total	81	120

*Definite FH = DLCN score >8; Probable FH = DLCN score 6 to 8; and possible FH = DLCN score 3 to 5.
†Statistically significant ($P < 0.05$ at 95% CI).

Effect on Lipids

The LDL-C levels were examined on a median of 6 (1-26) occasions during follow-up. Median (IQR) LDL-C, TG, HDL-C, and TC:HDL-C ratio in primary prevention patients at the initiation of PCSK9-i (evolocumab) were 4.4 (3.7-5.2) mmol/L, 1.9 (1.2-2.6) mmol/L, 1.2 (1.1-1.4) mmol/L, and 4.8 (3.6-6.0) mmol/L, respectively. In secondary prevention, the median (IQR) of LDL-C, TG, HDL, and TC:HDL-C ratio at the initiation of evolocumab were 3.6 (2.7-5.0) mmol/L, 1.9 (1.4-2.9) mmol/L, 1.2 (1.0-1.4) mmol/L, and 4.4 (3.5-5.5) mmol/L, respectively.

Overall, robust median (IQR) percent reductions in serum LDL-C of 46% (17.4%; 66.2%), TG of 17.8% (5.2%; 39.5%), and TC:HDL-C ratio of 32.1% (14.1%; 46.3%) (all, $P < 0.0001$) occurred in the first 90 days' postinitiation of evolocumab along with an increase in HDL-C (2.2% [–4.7%; 11.6%]; $P < 0.005$). In the primary prevention group, LDL-C was reduced by 43.7% (10.8%; 63.0%), TG by 15% (35.3%; 7.2%), and the TC:HDL ratio by 31.5% (11.1%; 46.0%) (all, $P < 0.0001$). In the secondary prevention group, the reductions in LDL-C were 48.3% (22%; 70%); TG, 19.6% (1.2%; 32.5%); and TC/HDL-C ratio, 32.6% (14.6%; 46.3%) (all, $P < 0.0001$). The median increase in HDL-C was 5.8% (–4.6%; 11.9% [$P < 0.0001$]) in the primary prevention group and 2% (–5.4%; 11.3% [$P < 0.05$]) in the secondary prevention group. Changes in LDL-C after initiation of evolocumab in the primary and secondary prevention groups are illustrated in Figure 5.

Statin Background

A robust path for LLT combinations was used before the clinical decision to initiate evolocumab; 70.4% (n = 57) of patients in the primary prevention group and 81.4% (n = 83) in the secondary prevention group received at least one statin therapy since the diagnosis of hyperlipidemia. Median duration of statin usage for patients treated with a statin before

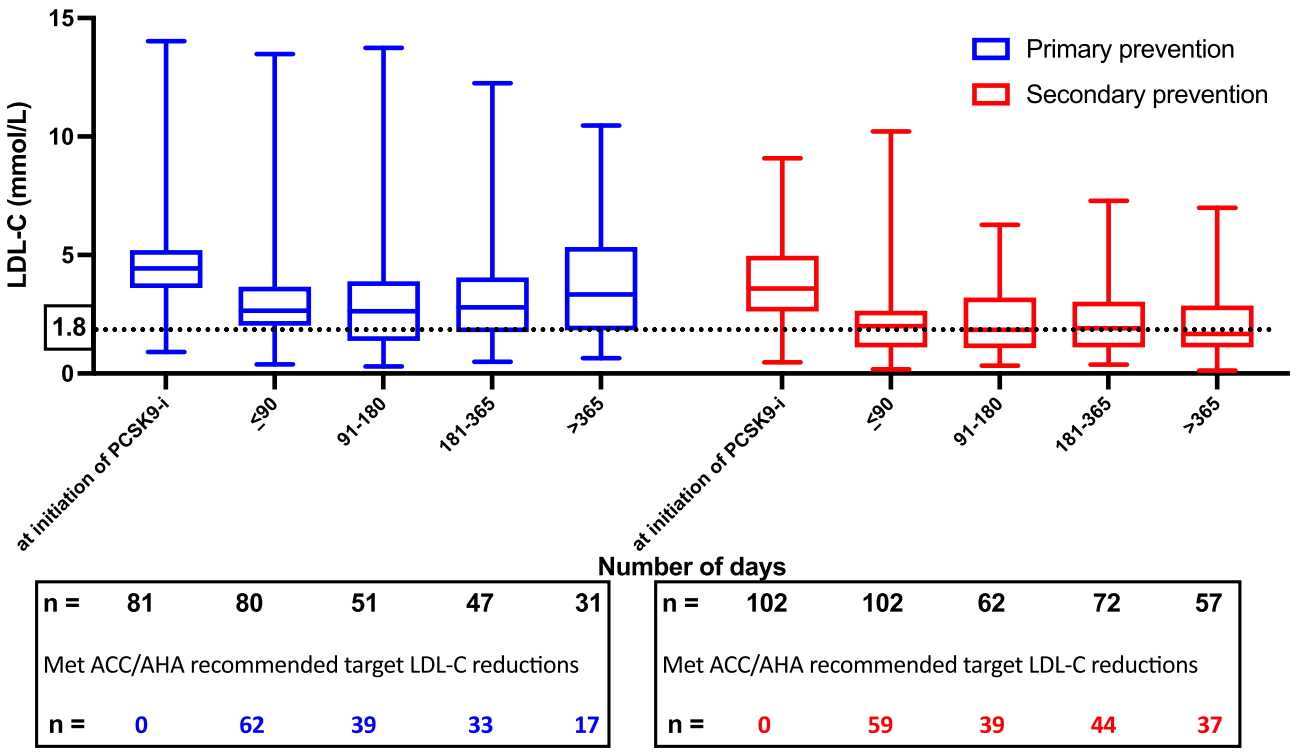

Figure 1. Reduction in LDL-C postinitiation of evolocumab. Values are presented as numbers, and median (IQR). Primary prevention group target ≥30% reduction or LDL-C <2.6 mmol/L; secondary prevention group target ≥50% reduction or LDL-C <1.8 mmol/L. n = number of patients at each time point. ACC/AHA = American College of Cardiology/American Heart Association; PCSK9-i = proprotein convertase subtilisin/kexin 9- inhibitor.

evolocumab initiation was 600 (267; 903) days in the primary prevention group and 568 (331; 836) days in the secondary prevention group. The chief reason for previous LLT discontinuation at initiation of evolocumab was statin intolerance in 33 (40.7%) patients in the primary prevention group and in 27 (26.5%) patients in the secondary prevention group ($P < 0.04$). Discontinuation of statin and background therapy would also account for nonachievement of LDL-C targets. Statin-induced AEs were recorded in 25 (24.5%) patients in secondary prevention and 12 (14.8%) in primary prevention ($P < 0.001$).

Safety

Four (2.2%) patients presented with AEs attributed to evolocumab, including injection site reaction in two (1.1%), one (0.6%) with myalgia, and one (0.6%) with elevation of liver enzymes. Table III provides a summary of the treatment-emergent AEs.

DISCUSSION

In our experience, countries in the MENA region rely on data from North American and European authorities for new drug approvals, and data regarding the safety and effectiveness of new therapies in Arabic populations are lacking. To our knowledge, the present study is the first real-world study describing experience with evolocumab in the MENA region in a large cohort of patients who were followed up for at least 1 year. Overall, evolocumab was well tolerated and provided robust and sustained reductions in proatherogenic lipids.

Real-world experience reports, including the ones of Nanchen et al,[16] Gürgöze et al,[17] Waldmann et al,[18] and Sbrana et al,[19] described evolocumab use in statin intolerance (10%–12%) and in patients with FH. Furthermore, indications for use were high ASCVD risk and heterozygous FH reported by Villa et al[20] and Toth et al,[21] respectively. In our cohort, FH,

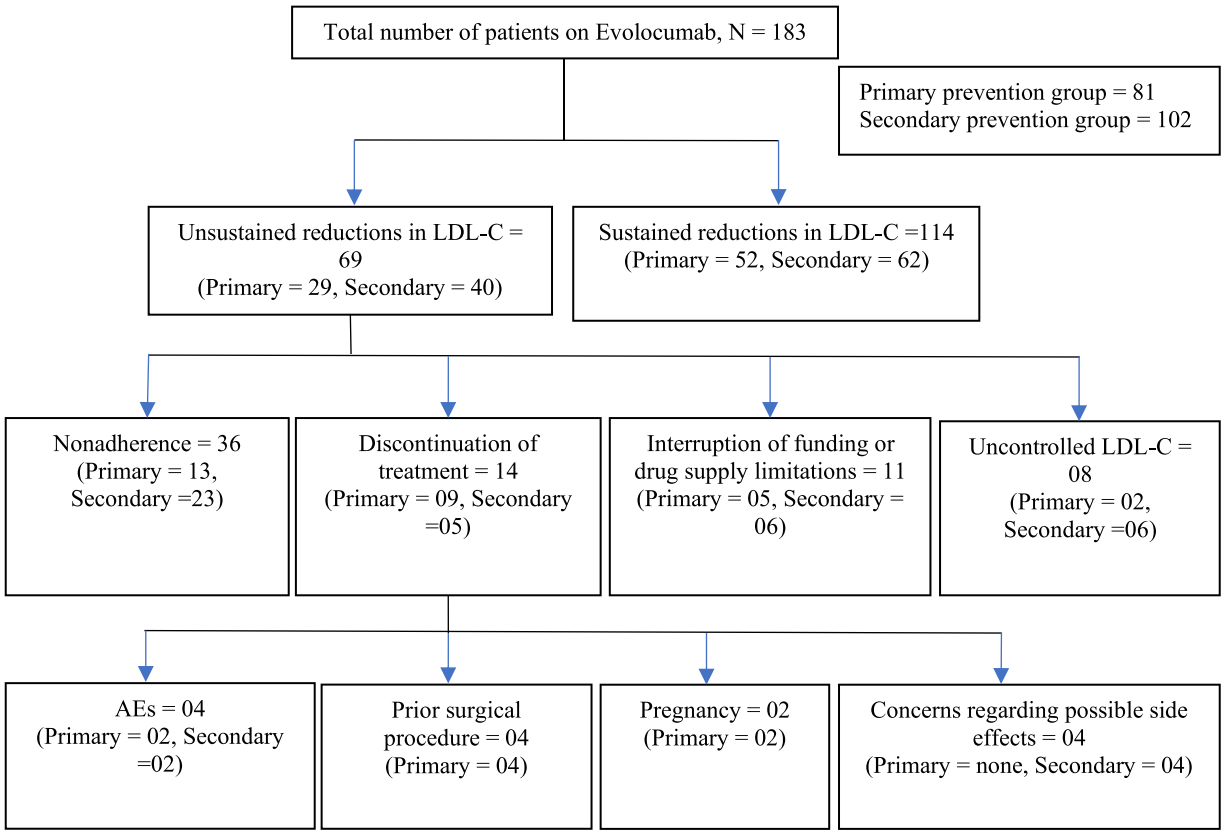

Figure 2. Flow diagram of study individuals treated with evolocumab according to sustained or not LDL-C reductions. Values are presented as numbers. AE = adverse events.

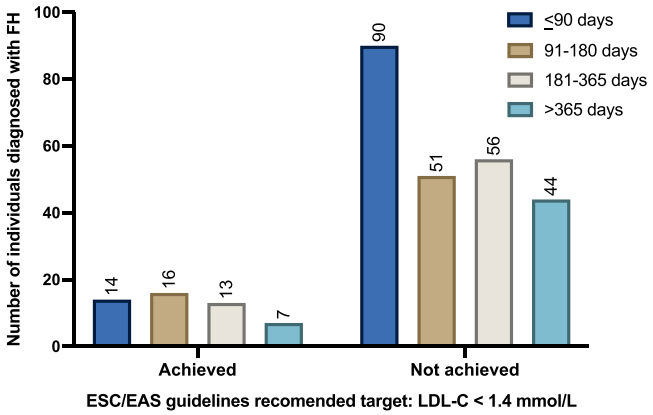

Figure 3. Individuals with definite familial hypercholesterolemia (FH) achieving LDL-C target <1.4 mmol/L. Values are presented as numbers. ESC/EAS = European Society of Cardiology/European Atherosclerosis Society.

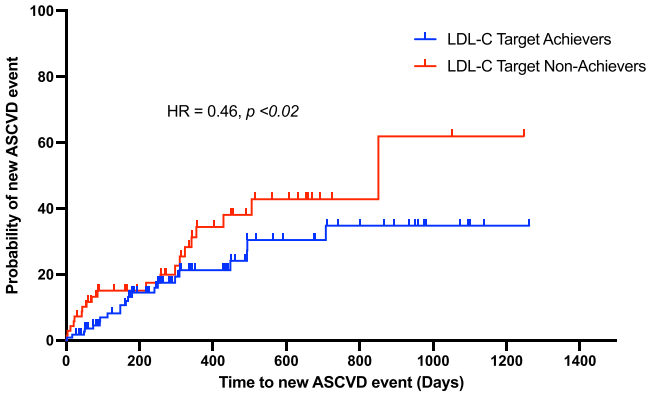

Figure 4. Kaplan-Meier curve analysis and Cox regression in LDL-C target achievers and nonachievers. Values are presented as number (%) or probability (%). ASCVD = atherosclerotic cardiovascular disease; HR = hazard ratio.

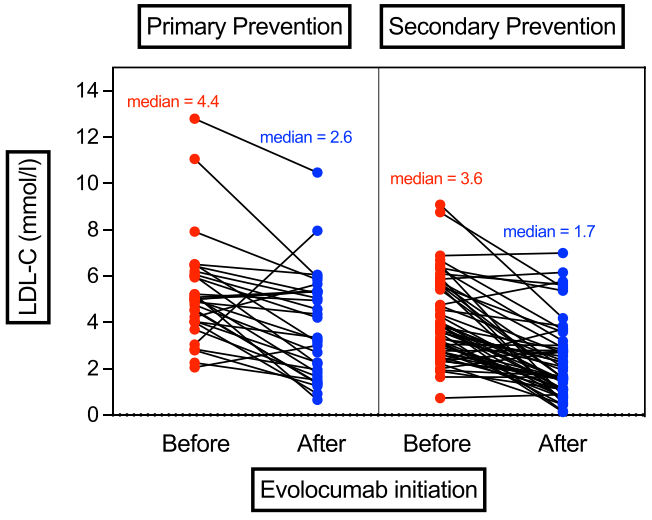

Figure 5. LDL-C before and after initiation of evolocumab (at >366 days) in individuals with previous or not atherosclerotic cardiovascular disease diagnosis. Follow-up period = >366 days. Primary prevention group, n = 31; secondary prevention group, n = 57.

Table III. Summary of treatment-emergent adverse events (TEAEs) for evolocumab.

TEAEs for Evolocumab	Primary Prevention (n = 81)	Secondary Prevention (n = 102)
Any TEAE, n (%)	2 (2.47%)	2 (1.96%)
One	2 (100%)	2 (100%)
More than one	None	None

very high ASCVD risk, and statin intolerance were the leading indications for the use of evolocumab. Evolocumab was effective in lowering LDL-C levels to within individualized target ranges in the majority of participants, particularly in those with statin intolerance.

Although significant LDL-C reductions were noted after evolocumab prescription in both the primary and secondary prevention groups, these reductions were more pronounced in the secondary prevention group. The most likely explanation is the higher number of FH patients in the primary prevention cohort who usually have higher baseline LDL-C levels. The high number of FH individuals with elevated LDL-C levels is difficult to treat, in case the induction of PCSK9 inhibitor with other LLT may benefit.[22] Other potential factors include a higher proportion of female patients, younger age, and higher baseline HDL-C and TG levels in the primary prevention group, which have been reported to independently affect the likelihood of achieving LDL-C targets.[23] We observed sustained reductions in LDL-C during evolocumab treatment comparable with those reported by Wasserman et al,[24] who also reported more stability of lipid lowering in those receiving standard doses of evolocumab.

Although up to a 70% reduction in LDL-C was reported in Phase III clinical trials,[25] and an expected up to 85% in triple LLT combination as stated in the ESC/EAS guidelines,[5] other real-world experience studies performed following regulatory approval of evolocumab reported LDL-C reductions averaging from 40% to 60%,[27–33] which is comparable to our findings. LDL-C reductions of 39%, 52.3%, 54.9%, and 60% were observed in PCSK9 treatment groups in reports by Sarsam et al,[26] Koren et al,[27] Santos et al,[28] and Desai et al.[29]

In the present study, introduction pf evolocumab helped attain the ACC/AHA guidelines- recommended reduction in LDL-C (≥30% reduction or LDL-C <2.6 mmol/L in primary prevention or ≥50% reduction or LDL-C <1.8 mmol/L in secondary prevention) not only as add-on therapy to statins but also as a combination with other LLTs in statin-intolerant patients. Voutyritsa et al[34] reported greater (up to 70%) reductions in LDL-C with evolocumab when administered with other LLTs. Desai et al[29] observed an LDL-C reduction of up to 60% in a real-world setting. Gürgöze et al[17] reported that the addition of evolocumab to other LLTs lowered LDL-C levels by ∼60%.

The secondary outcome measure of the present study was the incidence of ASCVD and/or cardiac events postinitiation of evolocumab. The incidence of new ASCVD events in patients at a minimum follow-up of 366 days was 8.6% and 29.4%, respectively, in the primary and secondary prevention groups. These findings clearly highlight the elevated ASCVD risk and great unmet need of the studied population. How much the use of evolocumab in our population has had an impact on the risk of these events remains to be determined. Previously, Dixon et al[30] reported a 9.8% reduction in the incidence of ASCVD events after initiation of evolocumab in patients at high risk of ASCVD already treated with statins. In contrast, among the secondary prevention patients, only the FOURIER trial reported a 15% reduction in ASCVD incidence (hazard ratios of 0.83 and 0.87 in patients with diabetes and without diabetes, respectively).[31] Due to the lack of a comparison group in our study, we are unable to comment on relative risk reduction in ASCVD incidence.

Evolocumab was well tolerated, with few documented AEs in our patients. Similar good tolerability has also been shown in the GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3) randomized clinical trial,[32] which reported a significant reduction in LDL-C levels with evolocumab and also fewer AEs compared with other LLTs. Based on our findings, we suggest that evolocumab is a well-tolerated, safe drug for the treatment of hyperlipidemia in patients with or without cardiac comorbidities.

Gürgöze et al[17] noted that drug discontinuation was responsible for a nonsustained LDL-C reduction in 7% of participants. We observed comparable rates of evolocumab discontinuation but a smaller proportion was attributed to AEs (2.2%). In contrast, the OSLER-1 (Open Label Study of Long Term Evaluation Against LDL-C Trial) extension study[33] reported discontinuation of evolocumab in 21% of participants.

The current study is the first from the MENA region that reports the real-world efficacy of evolocumab in a mixed risk population of individuals with FH and other non-FH indications. Notable strengths of our study include a relatively large cohort, patient heterogeneity and high retention, and a minimum follow-up of 1 year. Despite these strengths, our study has some limitations,

including the selection bias due to the retrospective design and absence of comparative group.

CONCLUSIONS

Clinically meaningful and sustained reductions in LDL-C, TG, and cholesterol ratios were observed after introduction of evolocumab, and the drug was well tolerated. This supports the role of evolocumab in the management of hyperlipidemia and ASCVD in a predominantly Arabic population.

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DECLARATION OF INTEREST

Dr. Santos has received honoraria related to consulting, research, and or speaker activities from: Abbott, Amgen, Aché, AstraZeneca, Esperion, EMS, GETZ Pharma, Kowa, Libbs, Merck, MSD, Novo Nordisk, Novartis, PTC Therapeutics, Pfizer, Roche, and Sanofi. Dr. Sabbour has received honoraria related to speaker activities from: Abbott, Amgen, AstraZeneca, Libbs, Merck, MSD, Novo Nordisk, Novartis, Pfizer, Roche, and Sanofi. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.08.005.

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