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Evolocumab safety and efficacy in hypercholesteremia patients with or without diabetes: a retrospective real-world analysis

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Abstract

Background Proprotein convertase subtilisin/kexin type 9 inhibitors effectively reduce LDL cholesterol and adverse cardiovascular events with a safety profile comparable to a placebo. Limited real-world data exists on their effectiveness in different patient groups. This study evaluated evolocumab's efficacy and safety in hypercholesteremia patients with and without diabetes.

Method In a large tertiary hospital in Saudi Arabia, patients aged 18 and above who initiated evolocumab therapy were screened for eligibility between January 2017 and July 2023. All patients who had been on maximally tolerated statin and ezetimibe therapy for at least 4 months before starting evolocumab were included. The included participants were then divided into diabetic and non-diabetic groups and assessed for evolocumab's efficacy and safety. Efficacy was measured by LDL-C reduction and target achievement, while safety was assessed by examining glycemic control changes, new-onset diabetes (NOD) and hepatic enzyme levels. Data analysis included descriptive and comparative methods, with significance set at $p < 0.05$.

Results A total of 151 patients were included, with an average age of 51.77 years. The majority of patients were male (67.6%) and obese (81.5%). Around 55% had diabetes, and 63% had established atherosclerotic cardiovascular disease at baseline. During a mean follow-up period of 13.17 months, the average reduction in LDL-C from baseline was − 34.21, − 28.66, and − 39.61% for the overall cohort, non-diabetic patients, and diabetic patients, respectively. In the overall cohort, 34.4 and 24.5% reached the target LDL-C levels of less than 1.4 mmol/L (55 mg/dL) and less than 1.8 mmol/L (70 mg/dL), respectively. Worsening of glycemic control (HbA1C increase > 0.5) was observed in 25.83% of the overall cohort, 16.18% of non-diabetics, and 33.74% of diabetics. An HbA1C increase > 1 was observed in 13.25% of the overall cohort, 2.94% in non-diabetics and 21.69% in diabetics. Five patients (3.3%) developed NOD.

Conclusion The study demonstrated that the addition of evolocumab to maximally tolerated statin and ezetimibe therapy reduced LDL-C levels but with a smaller average reduction and a lower proportion of patients achieving recommended LDL-C targets than in landmark clinical trials. Additionally, there was a potential negative effect on glycemic control, warranting further investigation.

Keywords LDL-C, Hypercholesterolemia, Evolocumab, Statin, Ezetimibe, Glycemic control, Diabetes

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Introduction

Hypercholesterolemia or elevated low-density lipoprotein cholesterol (LDL-C) is a well-established, strong, and independent modifiable risk factor for the development of atherosclerotic cardiovascular disease (ASCVD) in adults [1, 2]. Interventions aimed at aggressively curbing the consequences that LDL-C has on cardiovascular (CV) morbidity and mortality are of great importance [3].

The three mainstays of LDL-C-lowering therapy are high-intensity statin therapy, ezetimibe, and PCSK9 inhibitors. Current guidelines advocate for stringent LDL-C targets with > 50% LDL-C reductions for those at high cardiovascular risk and those with established ASCVD. To achieve the desired LDL-C levels, a sequential approach is recommended, beginning with high-intensity statins, followed by ezetimibe and, potentially, PCSK9 inhibitors [3–5].

PCSK9 inhibitors, such as evolocumab, were FDA-approved in 2015 for patients with ASCVD who need additional LDL-C reduction despite maximally tolerated statin therapy [6]. Administered subcutaneously every two or four weeks, these monoclonal antibodies target PCSK9, a protein involved in cholesterol metabolism. By preventing PCSK9 from binding to LDL receptors on liver cells, these inhibitors protect the receptors from degradation, enhancing the liver's ability to remove LDL-C from the bloodstream. This mechanism leads to significant LDL-C reductions of about 60% [7–9].

Furthermore, PCSK9 inhibitors have demonstrated cardiovascular benefits in high-risk patients with ASCVD. The FOURIER trial, involving 27,564 patients, found that evolocumab added to statin therapy reduced the risk of major adverse cardiovascular events (MACE) by 15% [10]. Similarly, the ODYSSEY trial, with 18,924 patients who had recent ACS, showed that alirocumab plus statin led to a 15% reduction in MACE and all-cause mortality [11]. Both trials reported no significant side effects or safety concerns. However, it should be noted that the duration of these trials was relatively short, with a median follow-up of approximately 78 weeks, which is not adequate to prove long-term safety.

Recent emerging studies examining the effects of LDL-C-lowering genetic variations in PCSK9, which mimic the action of PCSK9 inhibitors, have indicated a potential increase in new-onset diabetes (NOD) risk. Genetic variants in PCSK9 and HMGCR show comparable impacts on NOD risk for every 10 mg/dL decrease in LDL-C. Specifically, a 10 mg/dL reduction in LDL-C is associated with an odds ratio (OR) of 1.11 for PCSK9 and 1.13 for HMGCR. Lower LDL-C levels linked to PCSK9 variants are also associated with higher fasting glucose levels and a 29% increased likelihood of NOD [12, 13].

The most extensive and reliable data on PCSK9 inhibitors and hyperglycemic conditions comes from the FDA Adverse Event Reporting System (FAERS). Analysis of these data shows a higher reporting of hyperglycemia with PCSK9 inhibitors compared to the overall database, with 2.1% of reports mentioning hyperglycemia. However, most of these reports are for mild hyperglycemia, not diabetes. Diabetic patients treated with PCSK9 inhibitors experience hyperglycemia more often than non-diabetic patients, with rates of 11.3 and 9.9% for evolocumab and alirocumab, respectively, compared to 2.1 and 1.3% in non-diabetic patients [14].

Real-world knowledge and experience with PCSK9 inhibitors are still in their infancy, with long-term safety issues yet to be discovered. Therefore, this study aimed to investigate evolocumab's efficacy and safety in high-CV-risk patients with or without diabetes. Another aim of the study was to determine the factors associated with achieving LDL-C Target.

Methods

Study design and participants

This was a single-center, retrospective study conducted at King Abdulaziz Medical City, located in Riyadh, Saudi Arabia. The list of patients who received evolocumab from January 2017 to July 2023 was extracted from the institution's electronic medical records and screened for inclusion. Patients aged ≥ 18 years who have been on maximally tolerated statin therapy plus ezetimibe for at least 4 months before starting evolocumab and have had at least 12 months of evolocumab exposure were included. Patients were excluded if not receiving maximally tolerated statin therapy along with ezetimibe for at least four months prior to initiation of evolocumab therapy, with less than 12 months exposure to evolocumab therapy, with recent (< 4 months) lipid-lowering regimen modification, lost in follow-up, with missing baseline data (lipid profile, HbA1C, or liver function tests), with abnormal liver function tests at baseline, or prescribed lipid-lowering therapies other than high-intensity statin therapy and ezetimibe along with evolocumab at baseline. The exclusion criteria included also discontinuation or changing the lipid-lowering therapy, including statin, ezetimibe, and evolocumab. Eligible patients were then categorized into two groups, "patients with diabetes" and "patients with no diabetes" at baseline, and were retrospectively assessed for evolocumab efficacy and safety.

Data were collected from patient medical records up to 12 months prior to evolocumab therapy initiation and at least up to 12 months post-evolocumab initiation,. Data collection ended on July 31, 2023. This study was approved by the Institutional Review Board of King Abdullah International Medical Research Center

(IRB/0822/23.). Informed consent from the participants was waived due to the retrospective nature of the study.

Study outcomes

The efficacy outcomes were the reduction in LDL-C after starting evolocumab, the proportion of patients achieving at least a 50% reduction in LDL-C from baseline, and the percentage of patients meeting the 2019 ESC/EAS dyslipidemia guidelines' recommended LDL-C targets of less than 1.8 mmol/L (< 70 mg/dL) and less than 1.4 mmol/L (< 55 mg/dL) in patients with ASCVD and/or familial hypercholesterolemia [4].

Safety outcomes included rate NOD (among patients with no diabetes diagnosis at baseline), worsened glycemic control in the overall study cohort, and rate of hepatic enzyme elevations throughout follow-up. NOD was defined as the first time that a diabetes diagnosis was confirmed (HbA1c ≥ 6.5%), worsening of glycemic control in patients with or without diabetes diagnosis at baseline was determined by either a rise in HbA1c by ≥ 0.5 or 1.0 from baseline at any time during the entire follow-up period, increase in the number of diabetes medications throughout follow up compared with baseline, and increase in number of insulin users throughout follow up compared with baseline. Abnormal laboratory results defined as alanine aminotransferase (ALT) ≥ 2X upper normal limit (UNL) or ≥ 3X UNL throughout follow-up were also observed as a safety outcome parameter.

Statistical analysis

All data collected were combined in an electronic data collection sheet using Excel version 16.58, 2019. The data were entered into SPSS version 21 for Windows (SPSS) for analysis. Descriptive analysis was used, with categorical variables being reported as numbers and percentages, with continuous variables reported as mean (± SD and 95% CI). Data was analyzed descriptively and comparatively. Descriptive data was presented as Means (SD) or frequencies (percentages). Chai square or Fisher's Exact tests with crosstabulation were used to compare proportions among categorical groups. For continuous variables, the student's-t test was used to compare means between two groups. Univariate logistic regression was used to assess the association between various demographic and clinical factors with primary outcomes, and the odds ratio (OR) was computed as applicable. A p-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Out of the 642 patients who were screened for eligibility, 151 met the inclusion criteria and were enrolled in this study. The majority of the study cohort were male (67.6%), aged 51.8 ± 12.4 years, 29% were active smokers, 13.9% were former smokers, 81.5% were obese, 25.3% had a family history of coronary heart disease, 49% had hypertension, 55% had diabetes, 13.2% had familial hypercholesteremia (FH), had a mean of 3.04 ± 1.25 ASCVD risk factors, 67% had established ASCVD, and 49% had a prior revascularization intervention, (Table 1) illustrate further details on the baseline characteristics. Additional comorbidities noted in the cohort included heart failure with reduced ejection fractions (HFrEF) (15.2%), anemia (15.2%), asthma (7.3), chronic kidney disease (CKD) (8.6%), and hypothyroidism (12.6%).

Common concomitant cardiac medications include aspirin (70.2%), angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (62.3%), beta-blockers (56.3%), clopidogrel (31.1%), calcium channel blockers (22.5%), and isosorbide dinitrate (15.9%). The most commonly prescribed non-insulin diabetes medication at baseline was metformin (88%). Other frequently prescribed diabetes medications included gliclazide MR (39.8%), dapagliflozin (43.4%), sitagliptin (50.6%), semaglutide (21.7%), liraglutide (3.6%), dulaglutide (1.2%), pioglitazone (3.6%), and insulin (60.2%). It's important to note that some patients without diabetes were prescribed these medications at the beginning of the study for non-diabetes reasons. For example, 14.7% of patients were prescribed metformin for prediabetes, 5.9% were prescribed semaglutide for obesity to help with weight reduction alongside lifestyle and dietary interventions, and 10.3% were prescribed dapagliflozin for cardiac (i.e., HFrEF) or renal (i.e., CKD) conditions. Further details are presented in (Supplementary Table S1).

Lipid-lowering therapy at baseline

The majority of the study cohort (57%) was prescribed high-intensity rosuvastatin dosing at baseline, while only 3.3% were on high-intensity atorvastatin dosing. 17.9% were on moderate-intensity rosuvastatin dosing, 14.6% were on moderate-intensity atorvastatin, and 7.3% were on either low-intensity atorvastatin or rosuvastatin. There were statistical differences in statin prescriptions at baseline between diabetic patients and nondiabetic patients ($P = 0.321$) (Supplementary Table S1). The mean duration of statin use before evolocumab initiation was 49.15 months for the entire cohort, 46.88 months for non-diabetic patients, and 50.58 months for diabetic patients. The average duration of ezetimibe use prior to evolocumab was 24.23 months, 26.37 months, and 22.47 months for the entire cohort, non-diabetic patients, and diabetic patients, respectively. The mean duration of evolocumab exposure throughout the follow-up was 23.17 months, with a mean of two follow-up visits after the baseline visit where evolocumab was initiated. The

Table 1 Baseline Characteristics

Characteristics	Overall (n = 151)	Non-DM (n = 68)	DM (n = 83)	P-value
Demographics				
Mean age-y, mean (SD)	51.77 (12.39)	47.29 (13.59)	55.45 (9.98)	< 0.001*
Age group (years)				
18–29 year, n (%)	9 (6.0)	9 (13.2)	0 (0.0)	< 0.001
30–39 year, n (%)	10 (6.6)	7 (10.3)	3 (3.6)	
40–59 year, n (%)	90 (59.6)	40 (58.8)	50 (60.2)	
60–69 year, n (%)	31 (20.5)	11 (16.2)	20 (24.1)	
> 70 year, n (%)	11 (7.3)	1 (1.5)	10 (12.0)	
Gender				
Female, n (%)	49 (32.5)	21 (30.9)	28 (33.70	0.710
Male, n (%)	102 (67.5)	47 (69.1)	55 (66.3)	
eGFR-ml/min/1.73 m^2, mean (SD)	102.97 (33.07)	110.84 (34.19)	96.52 (30.84)	0.008*
Baseline ASCVD risk profile				
BMI, mean (SD)	29.82 (5.85)	28.62 (5.62)	30.79 (5.89)	0.022*
Body weight, mean (SD)	81.11 (17.77)	84.99 (19.48)	77.93 (15.65)	0.017*
Obese (> 30 kg/m^2), n (%)	70 (46.4)	25 (36.8)	45 (54.2)	0.032
Familial hypercholesterolemia, n (%)	20 (13.2)	9 (13.2)	11 (13.3)	0.997
Smoking history				
Non-smoker, n (%)	86 (57.0)	45 (66.2)	41 (49.4)	0.114
Former-smoker, n (%)	21 (13.9)	7 (10.3)	14 (16.9)	
Smoker, n (%)	44 (29.1)	16 (23.5)	28 (33.7)	
Positive family history for ASCVD, n (%)	38 (25.2	15 (22.1)	23 (27.7)	0.426
Diabetes, n (%)				
Hypertension, n (%)	74 (49.0)	22 (32.4)	52 (62.7)	< 0.001
ASCVD risk factors number at baseline, mean (SD)**	3.04 (1.25)	2.13 (0.96)	3.78 (0.94)	< 0.001*
Baseline Comorbid CV diseases				
Chronic Stable IHD n (%)	10 (6.6)	1 (1.5)	9 (10.8)	0.023
Unstable Angina n (%)	6 (4.0)	1 (1.5)	5 (6.0)	0.223
STEMI n (%)	24 (15.9)	12 (17.6)	12 (14.5)	0.594
HFrEF (EF ≤ 40%), n (%)	23 (15.2)	9 (13.2)	14 (16.9)	0.537
Atrial fibrillation, n (%)	8 (5.3)	4 (5.9)	4 (4.8)	1.000
Stroke/TIA, n (%)	5 (3.3)	3 (4.4)	2 (2.4)	0.658
History of Re-vascularization				
Prior history of CABG, n (%)	24 (15.9)	13 (19.1)	11 (13.3)	0.327
Prior history of PCI, n (%)	50 (33.1)	18 (26.5)	32 (38.6)	0.116

*student's t-test, others Chi-square test

**Risk factors counted include dyslipidemia and DM; dyslipidemia was not included separately in these analyses because all patients in the study had dyslipidemia

mean follow-up period length was 13.17 months for the entire cohort, 14.13 months for non-diabetics, and 12.39 months for diabetics.

LDL-C levels measurements at baseline

In the overall cohort, 88.1% of patients had LDL-C above 2.6 mmol/L (100 mg/dL), 98.7% had LDL-C above 1.8 mmol/L (70 mg/dL), and all patients had LDL-C above 1.4 mmol/L (55 mg/dL). The average LDL-C level at baseline for the overall study cohort was 4.56 ± 2.46 mmol/L (176.34 ± 95.13 mg/dL), 5.13 ± 3.26 mmol/L (198.38 ± 126.1 mg/dL) for patients with no diabetes, and 4.09 ± 1.37 mmol/L (158.16 ± 52.98 mg/dL) for patients with diabetes.

Efficacy outcomes

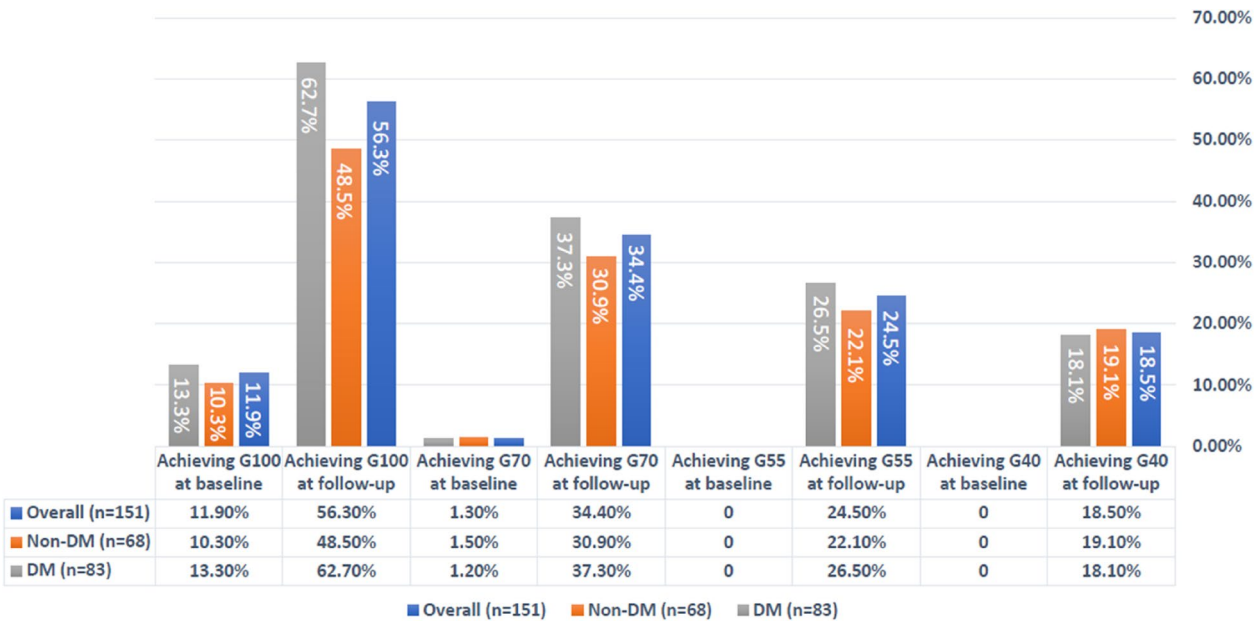
After an average follow-up of 13.17 months, the mean LDL-C levels decreased to 3.00 ± 2.54 mmol/L (116.01 ± 98.22 mg/dL), 3.66 ± 3.34 mmol/L (141.53 ± 129.16 mg/dL), and 2.47 ± 1.45 mmol/L (95.52 ± 56.1 mg/dL) for the entire cohort, non-diabetic patients, and diabetic patients, respectively. The percent

reduction in LDL-C from baseline was − 34.21, − 28.66, and − 39.61% for the overall cohort, non-diabetic patients, and diabetic patients, respectively.

A substantial reduction in LDL-C levels of more than 50% from baseline was achieved by 52.32% of the overall cohort, 51.47% of non-diabetic patients, and 53% of diabetic patients. In the overall cohort, 24.5 and 34.4% reached the target LDL-C levels of less than 1.4 mmol/L (55 mg/dL) and less than 1.8 mmol/L (70 mg/dL), respectively (Fig. 1). Among non-diabetic patients, 22.1 and 30.9% attained these targets, while among diabetic patients, 26.5 and 37.3% achieved the respective LDL-C targets (Table 2).

Potential determinants of LDL-C target levels attainment

In the overall study cohort, hypertensive patients had approximately significantly higher odds of attaining the target LDL-C levels of < 2.6 mmol/L (< 100 mg/dL) (OR 2.8, *P-value = 0.002)* and < 1 mmol/L (< 40 mg/dL) (OR 2.6, *P-value = 0.027*) compared to those without hypertension. Similarly, Patients with a history of NSTEMI had significantly higher odds of achieving the target



	Achieving G100 at baseline	Achieving G100 at follow-up	Achieving G70 at baseline	Achieving G70 at follow-up	Achieving G55 at baseline	Achieving G55 at follow-up	Achieving G40 at baseline	Achieving G40 at follow-up
Overall (n=151)	11.90%	56.30%	1.30%	34.40%	0	24.50%	0	18.50%
Non-DM (n=68)	10.30%	48.50%	1.50%	30.90%	0	22.10%	0	19.10%
DM (n=83)	13.30%	62.70%	1.20%	37.30%	0	26.50%	0	18.10%

Fig. 1 % LDL-C Target Achievement by the End of Follow-up. G: Goal; DM: diabetes mellitus; NDM: none diabetes mellitus

Table 2 Changes from baseline in lipid measures following evolocumab

Lipid profile	Overall (n = 151) M (± SD)	Non-DM (n = 68) M (± SD)	DM (n = 83) M (± SD)	P value
Baseline LDL	4.56 (± 2.46)	5.13 (± 3.26)	4.09 (± 1.37)	0.016
Post evolocumab (first follow-up)	3.00 (± 2.54)	3.66 (± 3.34)	2.47 (± 1.45)	0.008
Change in LDL	1.55 (± 1.53)	1.47 (± 1.38)	1.62 (± 1.64)	0.555
Percent change in LDL	34.73 (± 36.55)	31.42 (± 39.82)	37.45 (± 33.63)	0.369 *
Baseline TC	6.19 (± 2.35)	6.56 (± 2.93)	5.90 (± 1.68)	0.101
Post evolocumab (first follow-up) TC	4.66 (± 2.54)	5.30 (± 3.30)	4.13 (± 1.53)	0.008
Change in TC	1.54 (± 2.15)	1.27 (± 2.44)	1.77 (± 1.86)	0.154
Baseline HDL	1.06 (± 0.29)	1.10 (± 0.35)	1.02 (± 0.22)	0.098
Post evolocumab (first follow-up) HDL	1.06 (± 0.29)	1.11 (± 0.32)	1.01 (± 0.25)	0.076
Change in HDL	0.002 (± 0.22)	− 0.001 (± 0.23)	0.004 (± 0.20)	0.879
Baseline TG	2.16 (± 1.43)	1.84 (± 1.37)	2.42 (± 1.44)	0.012
Post evolocumab (first follow-up) TG	1.77 (± 1.19)	1.56 (± 1.31)	1.95 (± 1.10)	0.046
Change in TG	0.39 (± 1.25)	0.28 (± 0.95)	0.48 (± 1.45)	0.343

*Wilcoxon test, all others were Student-t test, DM: diabetes mellitus, NDM: none diabetes mellitus

LDL-C levels of < 2.6 mmol/L (< 100 mg/dL) (OR 2.44, *P-value = 0.011),* < 1.8 mmol/L (< 70 mg/dL) (OR 2.03, *P-value = 0.043*). Additionally, a history of prior PCI was significantly associated with higher odds of achieving target LDL-C levels of < 2.6 mmol/L (< 100 mg/dL) (OR 3.14, *P-value = 0.002*), < 1.8 mmol/L (< 70 mg/dL) (OR 3.57, *P-value = < 0.001*), and < 1 mmol/L (< 40 mg/dL) (OR 2.43, *P-value = 0.021*) (Table 3).

Patients with a baseline LDL-C level > 4.9 mmol/L (> 190 mg/dL) were less likely to achieve LDL-C targets of < 2.6 mmol/L (< 100 mg/dL) (OR 0.223, *P-value = < 0.001*), < 1.8 mmol/L (< 70 mg/dL) (OR 0.201, *P-value = < 0.001*), or < 1.4 mmol/L (< 55 mg/dL) (OR 0.372, *P-value = < 0.038*). Conversely, patients with a baseline LDL-C level < 2.6 mmol/L (< 100 mg/dL) had nearly three times the odds of achieving LDL-C targets of < 1.8 mmol/L (< 70 mg/dL) (OR 2.708, *P-value = 0.045*) and < 1.4 mmol/L (< 55 mg/dL) (OR 2.869, *P-value = 0.045*) compared to those with a baseline LDL-C level ≥ 2.6 mmol/L (≥ 100 mg/dL) (OR 1.644, *P-value = 0.344*).

For patients with diabetes, the use of rosuvastatin was associated with higher odds of attaining LDL-C targets of < 1.8 mmol/L (< 70 mg/dL) (OR 5.374, P-value = 0.007) and < 1.4 mmol/L (< 55 mg/dL) (OR 11.03, P-value = 0.006) compared to those taking atorvastatin. Patients with a baseline LDL-C level < 2.6 mmol/L (< 100 mg/dL) had approximately six times (OR 5.681, P-value = 0.016) the odds of achieving the LDL-C target of < 1.8 mmol/L (< 70 mg/dL) compared to those with a baseline LDL-C level ≥ 2.6 mmol/L (≥ 100 mg/dL) (Table 4).

Worsening of glycemic control

The mean baseline HbA1C of 7.41 ± 2.09, 5.68 ± 0.46, and 8.83 ± 1.81, for the overall cohort, patients with no diabetes, and patients with diabetes, respectively and remained almost unchanged with a mean HbA1C at follow-up of 7.40 ± 2.15, 5.72 ± 0.48, and 8.77 ± 2.01, for the overall cohort, patients with no diabetes, and patients with diabetes, respectively. Worsening of glycemic control, defined as an increase in HbA1C by > 0.5 observed at least once throughout follow-up, was observed in 25.83, 16.18, and 33.74% of patients among the overall cohort, patients with no diabetes, and with diabetes, respectively. A worsening of glycemic control, defined as an increase in HbA1C by > 1, was observed at least once throughout follow-up in 13.25, 2.94, and 21.69% of patients among the overall cohort, patients with no diabetes and with diabetes, respectively. By the end of follow-up, the average number of diabetes medications was non-significantly different from baseline (1.3 vs. 1.5). While the number of insulin users slightly increased from 60.24 to 67.47% of patients. Among patients without diabetes diagnosis at baseline, NOD was observed in five patients (3.3%) following evolocumab initiation (Table 5).

Rate of hepatic enzyme elevation

At a mean onset time of nearly one year following the initiation of evolocumab, ALT elevations of X2 UNL were observed in 3.3, 1.5, and 4.8% of patients in the overall study cohort, patients with no diabetes, and patients with diabetes, respectively. AST elevations of X2 UNL were observed in 2, 2.9, and 1.2% of patients in the overall study cohort, patients with no diabetes, and patients with diabetes, respectively.

Furthermore, ALT elevations of X3 UNL were observed in 1.3, 1.5, and 1.2% of patients in the overall study cohort, patients with no diabetes and patients with diabetes, respectively. AST elevations of X3 UNL were observed in 2, 1.5, and 2.4% of patients in the overall study cohort, patients with no diabetes, and patients with diabetes, respectively. (Supplementary Table S2).

Discussion

In this retrospective study, the safety and efficacy of the PCSK9 inhibitor evolocumab, when added to maximally tolerated statin and ezetimibe therapy, was evaluated in patients with hypercholesterolemia with and without diabetes, including high-risk patients being more than half of the study population who were receiving evolocumab for secondary prevention of ASCVD. The results indicated while the introduction of evolocumab to the current lipid-lowering regimen led to a reduction in LDL-C levels, the average reduction of 34.21% was less than anticipated. Additionally, the proportion of patients reaching the recommended LDL-C targets was lower than reported in clinical trials [10, 11]. The ODYSSEY OUTCOMES and FOURIER trials for alirocumab and evolocumab, respectively, have firmly established the enhanced LDL-C-lowering efficacy of PCSK9 inhibitor therapy. These landmark studies demonstrated a robust reduction in LDL-C levels, with reductions approaching 60% in some cases [10, 11]. However, it is crucial to recognize that the controlled environment of clinical trials, while essential for establishing the efficacy and safety of interventions, may not fully reflect the complexities and variations encountered in real-world clinical practice. In real-world settings, the use of PCSK9 inhibitors occurs within a less controlled framework, involving diverse patient populations with a range of comorbidities and adherence patterns. Additionally, the efficacy of these therapies may be influenced by factors such as ethnic and racial differences, which can impact the response to treatment and the overall management of dyslipidemia.

Table 3 Association (OR) between demographic and clinical factors with achievement of target LDL-C level at follow-up

	Overall (n = 151)								Non-DM (n = 68)								DM (n = 83)							
	G100 OR	P value	G70 OR	P value	G55 OR	P value	G40 OR	P value	G100 OR	P value	G70 OR	P value	G55 OR	P value	G40 OR	P value	G100 OR	P value	G70 OR	P value	G55 OR	P value	G40 OR	P value
Risk factors																								
Male gender	1.37	0.365	1.48	0.293	1.18	0.684	1.02	0.969	1.39	0.532	1.17	0.783	1.30	0.762	1.62	0.740	1.42	0.459	1.79	0.238	1.12	0.824	0.71	0.571
Smoking	1.53	0.243	1.12	0.749	0.72	0.458	0.61	0.320	2.10	0.201	1.02	0.971	0.42	0.292	0.53	0.718	1.11	0.826	1.13	0.795	0.88	0.824	0.66	0.52
Obesity (BMI ≥ 30)	0.95	0.894	0.98	0.971	0.97	0.954	0.21	0.583	0.96	0.947	1.08	0.879	0.82	0.755	0.72	0.754	0.587	0.780	0.84	0.713	1.01	0.971	0.49	0.222
Reduction in body weight	0.70	0.278	1.01	0.980	1.43	0.357	1.56	0.307	0.622	0.347	0.921	0.879	1.21	0.755	1.39	0.618	0.87	0.755	1.15	0.755	1.70	0.289	1.69	0.364
Age ≥ 60 year	1.58	0.219	1.65	0.176	1.58	0.253	1.92	0.133	2.48	0.166	2.73	0.168	1.22	0.719	1.53	0.568	1.04	0.923	1.19	0.707	1.70	0.289	2.39	0.126
Family history of CHD	1.46	0.324	0.604	0.223	0.496	0.149	0.30	0.051	0.91	0.870	0.27	0.122	0.20	0.161	0.75	0.57	2.02	0.189	0.85	0.765	0.70	0.542	0.60	0.542
Hypertension	2.80	0.002	1.70	0.122	1.75	0.143	2.61	0.027	3.33	0.025	1.96	0.216	1.54	0.538	2.08	0.324	2.10	0.108	1.42	0.459	1.85	0.254	4.83	0.034
Diseases																								
History of HFrEF (heart failure)	1.25	0.631	1.27	0.607	1.43	0.473	0.91	1.000	0.83	1.000	0.60	0.710	0.40	0.672	0.78	0.189	1.61	0.456	1.87	0.283	2.48	0.182	2.11	0.269
History of coronary artery disease																								
Chronic IHD (CHD)	1.18	1.000	1.29	0.737	1.35	0.707	1.99	0.395	0.50	1.000	0.68	1.000	0.77	1.000	0.80	1.000	1.21	0.793	1.39	0.722	1.44	0.693	2.58	0.353
Unstable Angina	1.58	0.696	0.95	1.000	1.57	0.635	2.29	0.308	0.47	0.485	0.68	1.000	0.77	1.000	0.80	1.000	0.88	0.900	1.12	0.900	1.93	0.605	3.33	0.220
NSTEMI	2.44	0.011	2.03	0.043	1.63	0.199	1.35	0.484	1.84	0.232	1.60	0.383	1.85	0.296	1.76	0.362	3.17	0.021	2.40	0.059	1.48	0.438	1.08	0.899
STEMI	2.11	0.117	1.77	0.200	1.33	0.562	1.19	0.753	2.48	0.166	1.78	0.493	1.22	0.719	1.53	0.687	1.95	0.521	1.84	0.350	1.47	0.724	0.89	1.000
History of prior revascularization																								
Prior PCI	3.14	0.002	3.57	< 0.001	2.43	0.021	2.01	0.097	2.76	0.073	3.17	0.041	2.28	0.198	2.02	0.306	3.17	0.021	3.76	0.005	2.46	0.072	2.09	0.194

Table 4 Association (OR) between demographic and clinical factors with achievement of target LDL-C level at follow-up Continue

	Overall (n = 151)								Non-DM (n = 68)								DM (n = 83)							
	G100 OR	P value	G70 OR	P value	G55 OR	P value	G40 OR	P value	G100 OR	P value	G70 OR	P value	G55 OR	P value	G40 OR	P value	G100 OR	P value	G70 OR	P value	G55 OR	P value	G40 OR	P value
Rosuvastatin use (Ref category Atorvastatin)	1.176	0.684	2.172	0.092	2.686	0.075	1.768	0.322	0.581	0.432	0.622	0.485*	0.609	0.680*	0.486	0.389*	2.050	0.152	5.374	0.007	11.03	0.006	6.255	0.061*
Worsening of glycemic control (change in Hba1c by more than 0.5), n (%)	0.618	0.209	0.668	0.335	0.542	0.210	0.645	0.410	0.667	0.735*	0.211	0.157*	0.349	0.439*	0.426	0.673*	0.462	0. 108	0.842	0.728	0.560	0.310	0.760	0.767*
Baseline LDL > 190 mg/dl (high risk patient)	0.223	< 0.001	0.201	< 0.001	0.372	0.038	0.451	0.126	0.084	< 0.001	0.062	0.001	0.109	0.026*	0.135	0.047*	0.425	0.084	0.363	0.069	0.703	0.542	0.938	1.000*
Achieving the target 100 mg/dl at baseline	1.644	0.344	2.708	0.045	2.869	0.045*	1.839	0.331*	0.775	1.000*	0.884	1.000*	1.477	0.645*	0.681	1.000*	3.035	0.197*	5.681	0.016*	4.200	0.060*	3.169	0.106*

OR: Crude odds ratio, Shaded cells indicate statistical significance; G: Goal; DM: diabetes mellitus; NDM: none diabetes mellitus

*Fisher's Exact test, all others were Chi-square, no one achieved the targets of G55 or G40 at baseline, so they were not included in analyses. The number who achieved the targets of 70 mg/dl at baseline was very few, so they were not included in analyses

Table 5 Worsening of Glycemic Control indicators

	Overall (n = 151)	Non-DM (n = 68)	DM (n = 83)	P value
Hba1c at baseline, mean (SD)	7.41 (± 2.09)	5.68 (± 0.46)	8.83 (± 1.81)	< 0.001**
Hba1c at follow-up, mean (SD)	7.40 (± 2.15)	5.72 (± 0.48)	8.77 (± 2.01)	< 0.001**
Average change in Hba1c, mean (SD)	0.01 (± 1.29)	−0.04 (± 0.32)	0.06 (± 1.72)	0.585**
Worsening of glycemic control (change in Hba1c by more than 0.5), n (%)	36 (23.8)	10 (14.7)	26 (31.3)	0.017
Onset from baseline in months, Mean (SD)	11.76 (± 6.66)	13.07 (± 7.18)	11.26 (± 6.53)	0.473**
New onset of diabetes, n (%)	5 (3.3)	5 (7.35)	0 (0.06)	
Onset from baseline in months, mean (SD)	15.73 (± 9.78)	15.6 (± 10.57)	–	–
Insulin use at baseline, n (%)	50 (33.1)	0 (0.0)	50 (60.2)	< 0.001
Insulin initiated during follow-up, n (%)	6 (4.0)	0 (0.0)	6 (7.2)	0.033 *
Number of diabetes medications used at baseline, mean (SD)	1.23 (± 1.24)	0.13 (± 0.38)	2.12 (± 0.94)	< 0.001**
Number of diabetes medications used by end of follow-up, mean (SD)	1.51 (± 1.39)	0.31 (± 0.55)	2.49 (± 1.06)	< 0.001**

DM: diabetes mellitus; NDM: none diabetes mellitus

*Fisher's Exact

**Student -t test, all others were Chi-square test

In comparison to other real-world studies, our study indicated that the proportion of patients achieving target LDL-C levels was relatively lower, with only 34.4 and 24.5% of patients reaching LDL-C levels below 1.4 mmol/L (55 mg/dL) and 1.8 mmol/L (70 mg/dL), respectively. Contrastingly, the German HEYMANS cohort study reported that 59% of their patients attained an LDL-C level less than 55 mg/dL, with 69% of those receiving background lipid-lowering therapy achieving this target and 49% of those not receiving such therapy also reaching the target [15]. Furthermore, the Canadian ZERBINI study, which involved 131 patients with hypercholesterolemia, found that evolocumab treatment resulted in a significant 58.7% reduction in LDL-C levels, with 77.5% of patients achieving the recommended LDL-C goal of < 1.8 mmol/L (70 mg/dL) [16]. It is important to note that the baseline LDL-C levels in both the HEYMANS and ZERBINI cohorts were significantly lower than in our study population. The median baseline LDL-C level in the HEYMANS cohort was 3.75 mmol/L (145 mg/dL) [15], and in the ZERBINI cohort, it was 3.5 mmol/L (135.3 mg/dL) [16], which is a considerable difference from the baseline LDL-C level of 4.56 mmol/L (176.34 mg/dL) observed in our study. This discrepancy in initial LDL-C levels could potentially influence the comparison of LDL-C reduction outcomes between the studies. It suggests that the higher baseline LDL-C levels in our study may have contributed to the lower rates of target LDL-C level attainment. Additionally, the discrepancy in response might also highlight potential interracial differences in how patients respond to treatment.

A recent study conducted in Saudi Arabia and Kuwait involved 225 adult participants, 155 of whom were from Saudi Arabia, as part of a multicenter ZERBINI study. The study revealed that evolocumab significantly reduced LDL-C levels by 57%- 62% in the first six months, with high persistence rates [17]. Although the study provides valuable insights into the use of evolocumab in a local clinical setting, it is unclear whether the observed response is solely due to evolocumab or if it is a result of maximizing other lipid-lowering therapies, as only 28% of the participants were on ezetimibe at baseline.

In terms of safety outcomes, findings from our study suggest that the initiation of evolocumab may lead to a deterioration in glycemic control, as evidenced by an increase in HbA1C levels. Specifically, across the entire cohort, patients without diabetes and those with diabetes, a worsening of glycemic control (defined by an HbA1C rise of > 0.5) was detected in 25.83, 16.18, and 33.74% of patients, respectively. Additionally, a more significant deterioration in glycemic control (an HbA1C increase of > 1) was observed in 13.25, 2.94, and 21.69% of patients within these respective groups. These findings were consistent with what was previously reported in a meta-analysis of 20 phase 2 and 3 randomized clinical trials that assessed the safety of PCSK9 inhibitors in comparison to placebo, where a significant mean increment of HbA1c of (0.032%) was observed in the evolocumab group. In this meta-analysis, the incidence of NOD did not appear to be elevated when compared to placebo, as evidenced by a relative risk of 1.04 (with a 95% CI 0.96 to 1.13) [18]. Our study found that five (3.3%) of the overall cohort developed NOD. This proportion appears to be within the range of previously reported, i.e., 1.2 to 8.8%. and appears to be nonsignificant when compared to placebo [19]. In a secondary analysis of the FOURIER study involving 25,982 patients, the relationship between lower LDL-C levels

and cardiovascular outcomes was examined, revealing a beneficial effect without an increased risk of NOD [20]. A post hoc analysis further confirmed the safety and efficacy of evolocumab in patients with and without diabetes, showing no increase in NOD incidence or changes in glucose and HbA1c levels over time [21]. The FOURIER open-label extension program, with a median follow-up of 7.1 years, also did not show an elevated risk of NOD with longer evolocumab exposure [22]. Recent evidence from real-world analysis by González-Lleó et al. assessing the effects of PCSK9 inhibitors on glycemic control and the development of NOD in patients with hypercholesterolemia. The study observed a slight, non-significant increase in fasting glucose levels and found a comparable incidence of NOD in patients treated with PCSK9 inhibitors relative to control groups. Notably, all cases of NOD occurred exclusively in patients who had prediabetes at the baseline of the study [23]. In our study, we observed a notably high prevalence of obesity among participants, with 81.5% classified as obese. This characteristic is particularly relevant given the established link between obesity and metabolic disorders, which can contribute to NOD. Additionally, approximately 55% of our cohort was in secondary prevention, indicating a population at higher cardiovascular risk. The presence of obesity and the significant proportion of patients with established cardiovascular disease may have influenced the outcomes observed in our study, particularly regarding glycemic control. It is essential to recognize that the metabolic state of these patients could affect their response to evolocumab and the overall management of their lipid levels. Future research should consider these demographic factors to better understand their implications on treatment efficacy and safety in diverse populations.

The current study also evaluated liver enzyme elevations, which were generally infrequent. Significant ALT elevations (≥ 3 UNL) were observed in 1.3% of the overall study cohort, 1.5% of patients without diabetes, and 1.2% of patients with diabetes. Similarly, AST elevations (≥ 3 UNL) were noted in 2% of the overall study cohort, 1.5% of patients without diabetes, and 2.4% of patients with diabetes. These elevations typically occurred around one year after the initiation of evolocumab.

In pre-marketing clinical trials, liver test abnormalities were rare among patients who received evolocumab, reported at rates comparable to placebo or standard care. Elevated serum ALT or AST (≥ 3 UNL) was observed in 0.4 to 1.8% of patients [24]. The marginally higher rates reported in our study might be due to the fact that all patients (100%) in this cohort were already on maximally tolerated statin and ezetimibe therapy, which are known for causing this side effect.

Limitations and strengths

The study has several limitations that should be considered when interpreting the findings. First, the retrospective nature of the study led to inconsistencies in data availability for all variables of interest. The absence of a control group makes it challenging to ascertain the causal relationship between evolocumab and changes in glycemic control. Additionally, lifestyle factors like diet and physical activity, socioeconomic status, or family history were not incorporated into the analysis of primary and secondary outcomes. The potential influence of these factors on glycemic control, development of NOD, and attainment of LDL-C target levels cannot be discounted, which may affect the generalizability of the study's conclusions. Another limitation is the lack of data on adherence to therapy, which is crucial for understanding treatment outcomes. While prescription refill data were used as a surrogate for adherence and persistence, this method does not provide definitive evidence of medication consumption. However, the study provides valuable insights into the effects of PCSK9 inhibitors on LDL-C levels, glycemic control, and the incidence of NOD in real-world settings, which can be more representative of actual patient outcomes than data from randomized controlled trials. Additionally, the study focuses on a specific and underexplored population, which is the Saudi population with and without diabetes. This targeted approach allows for a better understanding of the drug's effects in this particular demographic. By evaluating the efficacy and safety of evolocumab in a local context, the study can contribute to the development and refinement of dyslipidemia management guidelines that are tailored to the Saudi population. The study identifies gaps in current knowledge and practice, which can guide future research efforts to address these gaps and improve patient outcomes. A comparative study is needed to confirm the effect of evolocumab on glycemic control and NOD.

Conclusion

This study demonstrated that the addition of evolocumab to maximally tolerated statin and ezetimibe therapy resulted in a significant reduction in LDL-C levels; however, the average reduction was smaller, and the proportion of patients achieving the recommended LDL-C targets was lower than reported in landmark clinical trials. Additionally, our findings suggest a potential negative effect on glycemic control, as indicated by increases in HbA1C levels among patients. However, due to the retrospective nature of the study and the lack of a control group, these conclusions should be interpreted with caution. Further research, ideally with a controlled design, is warranted to clarify the impact of evolocumab on

glycemic control and to better understand its long-term safety and efficacy in diverse patient populations.

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CHD	Coronary heart disease
CHF	Chronic heart failure
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular diseases
DM	Diabetes mellitus
FH	Familial hypercholesterolemia
HFrEF	Heart failure with reduced ejection fraction
HMGCR	3-Hydroxy-3-methylglutaryl-coenzyme A reductase
LDL-C	Low-density lipoprotein cholesterol
NOD	New onset diabetes
NSTEMI	Non-ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PCSK9 inhibitors	Proprotein convertase subtilisin/kexin type 9 inhibitors
STEMI	ST-elevation myocardial infarction
TIA	Transient ischemic attack

Supplementary Information

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Supplementary Material 1

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Author contributions
Dr. Sultan Alraddadi contributed to the conceptualization, the manuscript's methodology, supervision, review, and editing. Dr. Hind Almodaimegh contributed to data curation and writing the original draft. Dr. Abdullah Alkharbosh contributed to data curation and writing the original draft. Dr. Hadeel Alharbi contributed to data curation and writing the original draft. Dr. Ahmed Fatherahman contributed to data curation and writing the original draft. Dr. Mona Alsheikh contributed to reviewing and editing the manuscript. Dr. Lama Alfehaid contributed to reviewing and editing the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of King Abdullah International Medical Research Center (IRB/0822/23). Due to its retrospective nature, informed consent from the participants was waived.

Competing interests
The authors declare no competing interests.

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