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Real-World safety and effectiveness of evolocumab in primary hypercholesterolemia and mixed dyslipidemia in Saudi Arabia

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A B S T R A C T

Introduction: Evolocumab's short-term efficacy and safety were proven in phase-3 clinical trial, but its long-term safety and effectiveness in the Saudi population are yet to be studied. The aim of this study was to assess the long-term safety and effectiveness of evolocumab in Saudi patients with primary hypercholesterolemia or mixed dyslipidemia.

Method: A retrospective cohort study evaluated adult patients who had newly been prescribed evolocumab for hypercholesterolemia or mixed dyslipidemia. Safety events included myocardial infarction, unstable angina, stroke, transient ischemic attack, heart failure, rhabdomyolysis, renal dysfunction, and myalgia. Effectiveness outcomes included changes in lipid profiles from baseline, assessed at 6-, 12-, 18-, and 24-month.

Results: The study sample were 469 who newly prescribed evolocumab, from which 69.1 % being male, were included. The most prevalent comorbidities were coronary artery disease, diabetes, and hypertension. Statin was the most commonly used therapy. The most common adverse events at 6-month follow-up, based on the incidence rate per 1000 person-years, were coronary revascularization (63.20), myalgia (44.96), myocardial infarction (31.53), unstable angina (31.49), heart failure (26.94), rhabdomyolysis without renal dysfunction (8.93), transient ischemic attack (4.46), and rhabdomyolysis with renal dysfunction (4.46). Stroke incidence increased with follow-up length, from 8.87 per 1000 person-years at 6 months to 12.84 per 1000 person-years at 24 months. Evolocumab use significantly reduced LDL and total cholesterol levels at 6, 12, 18, and 24 months follow-up, while having no significant effect on HDL or triglycerides levels.

Conclusion: Evolocumab appeared to be safe and effective therapeutic option for patients with primary hypercholesterolemia or mixed dyslipidemia to potentially reduce LDL levels to therapeutic levels when statins are insufficient.

1. Introduction

Hypercholesterolemia is one of the most common form of dyslipidemia that contribute to the development of cardiovascular diseases (CVD). (Karr, 2017; Trinder et al., 2020) Patients with hypercholesterolemia are twice as likely as people with normal total cholesterol levels to have CVD. (Karr, 2017) Low-density lipoprotein (LDL), the primary carrier of cholesterol to the arterial artery wall, is the most prevalent apolipoprotein B-containing lipoprotein in human plasma. Dyslipidemia, characterized by an increase in LDL cholesterol, increases cardiovascular risk, especially in atherosclerotic CVD. (Balling et al., 2020; Karr, 2017; Trinder et al., 2020) Research has demonstrated through epidemiological, clinical, and experimental studies that elevated LDL levels significantly contribute to the development of atherosclerosis.

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Consequently, one of the most widely used clinical practice strategies for ASCVD treatment and prevention is managing hypercholesterolemia especially by lowering LDL levels. (Su et al., 2021).

Randomized controlled trials have demonstrated a reduction in cardiovascular morbidity and mortality with high-efficacy lipid-lowering therapies. (Mach et al., 2020; Su et al., 2021) There are numerous therapeutic options for hypercholesterolemia, the first and most prevalent being statins which are recommended by several guidelines as first line therapy for cardiovascular risk reduction due to their low cost and high efficacy profile, with a predicted 50 % reduction in LDL level. (Grundy et al., 2019; Mach et al., 2020; Pearson et al., 2021) Real-world evidence, on the other hand, repeatedly reveals that a considerable proportion of patients at high risk of ASCVD or with established ASCVD fail to achieve the guidelines' target LDL values, while receiving recommended treatment. (Al Sifri et al., 2014; Allen et al., 2019; Gitt et al., 2017).

A humanized monoclonal antibody has been produced and designed to treat hypercholesterolemia by inhibiting the proprotein convertase subtilisin/kexin type 9 enzyme (PCSK9) which destroys LDL receptors and so indirectly modulates serum LDL level.(Roth and Davidson, 2018) PCSK9 inhibitors are well tolerated and produce considerable LDL reduction in hyperlipidemic people. (Karatasakis et al., 2017) Clinical trials of PCSK9 inhibitors, such as evolocumab and alirocumab, showed a reduction in LDL levels by 50–60 %. (Ginsberg et al., 2016; Hovingh et al., 2017; Kastelein et al., 2015; Raal et al., 2015) Thus, PCSK9 inhibitors are highly beneficial as add-on therapy to statin or when maximally tolerated statin therapy fails to lower LDL adequately or in people who are intolerant to statin therapy.

Since 2017, there was a notable increase in the utilization of PCSK9 inhbitors in Saudi Arabia. Given the notable variations in eligibility requirements for PCSK9 inhibitors therapy among countries, a deeper comprehension of the safety and effectiveness of PCSK9 inhibitors in real-world settings is imperative at the national level. (Blais et al., 2022) This study aims to evaluate the long-term safety and effectiveness of evolocumab in Saudi individuals with primary hypercholesterolemia and mixed dyslipidemia using real-world data.

2. Method

2.1. Study Design, Setting, and patients

This multicenter retrospective cohort study included patients treated at King Abdulaziz Medical City (KAMC), King Abdulaziz University Hospital (KAUH) and King Saud University Medical City (KSUMC), Saudi Arabia from January 2018 to June 2022. Adult patients who had newly prescribed evolocumab for hypercholesterolemia were included in this study. We excluded patients who were on plasmaapheresis, as well as those who had no baseline labs, follow-up labs, or clinic visits. The study was authorized by the institutional review boards (IRB) at KAMC (IRB/2629/21), KSUMC (E-22–7285) as well as KAUH (Reference No. 389–22). Informed consents also were obtained from participants before the enrollment in the study.

2.2. Data collection

The patients' electronic health records were reviewed to extract the following information: age and gender, past medical history, hypercholesterolemia therapies, and lipid profile at baseline and during subsequent follow-ups.

2.3. Outcomes

The safety outcomes included adverse events of interest such as myocardial infarction, unstable angina requiring hospitalization, stroke, transient ischemic attack, heart failure requiring hospitalization, rhabdomyolysis with or without renal dysfunction, and myalgia. The effectiveness outcomes include the mean differences in the lipid profile of total cholesterol, triglycerides, HDL, and LDL between the baseline which defined as the latest lipid profile data) (within 30 days) prior the the first prescription of evolocumab and subsequent follow-ups. The defined follow-ups were 6 months (182 ± 20 days), 12 months (365 ± 20 days), 18 months (547 ± 20 days), and 24 months (720 ± 20 days) from the first prescription of evolocumab.

2.4. Statistical analysis

Continuous and categorical data were described using descriptive statistics, mean with standard deviation (SD) or number with percentage (%). Person-years were gathered for all patients beginning with the initial evolocumab prescription and ending with the first occurrence of adverse events, withdrawal of evolocumab, or completion of the required follow-up time. The incidence rate was estimated based on the number of adverse events per person time at the given follow-up period and reported as per 1000 person-years with a 95 % confidence interval (CI). The mean difference in the lipid profile was computed using a paired *t*-test and provided with a 95 % confidence interval. For the statistical analysis, IBM SPSS software version 25 (IBM Corp., Armonk, NY, USA) was utilized.

3. Results

3.1. Patients' demographics and clinical Characteristics

The study comprised 469 individuals who were new users of evolocumab with 324 (69.1 %) being male and a mean age of 53.37 ± 13.93 years (Table 1). Comorbidities with the highest prevalence were coronary artery disease (61.4 %), diabetes (54.8 %), hypertension (54.8 %), myocardial infarction (28.8 %), and familial hypercholesterolemia (26.0 %). Statins were the most often utilized therapy with 88.9 % of the cohort using it. Other medications utilized by 6.6 % of the sample included fibrates, niacin, bile acid sequestrants, and PCSK9 inhibitors in addition to evolocumab (Table 1). Individuals' dispositions decreased over time during the follow-up period, with fewer individuals continuing to use evolocumab. Only 122 patients were on evolocumab medication after 24 months.(Fig. 1).

3.2. Safety outcomes

Table 2 summarizes the incidences of adverse events of interest. In

Table 1
Patient demographics, and clinical characteristic (N = 469).

Characteristic	Mean ± SD / number (%)
Age	53.37 ± 13.9
Gender (Male)	324 (69.1)
Comorbidities	
Hypertension	257 (54.8)
Diabetes mellitus	257 (54.8)
Metabolic Syndrome	75 (16.0)
Current Smoker	63 (13.4)
Former Smoker	36 (7.7)
Coronary artery disease	288 (61.4)
Myocardial infarction	135 (28.8)
Coronary-artery bypass grafting	106 (22.6)
Stroke	16 (3.4)
Peripheral-artery disease	3 (0.6)
Known familial hypercholesterolemia	122 (26.0)
Medication History	
Statins	417 (88.9)
Fibrates	14 (3.0)
Niacin	9 (1.9)
Bile acid sequestrants	5 (1.1)
PCSK9 inhibitors other than evolocumab	3 (0.6)

Data are presented as mean ± SD or number (%).

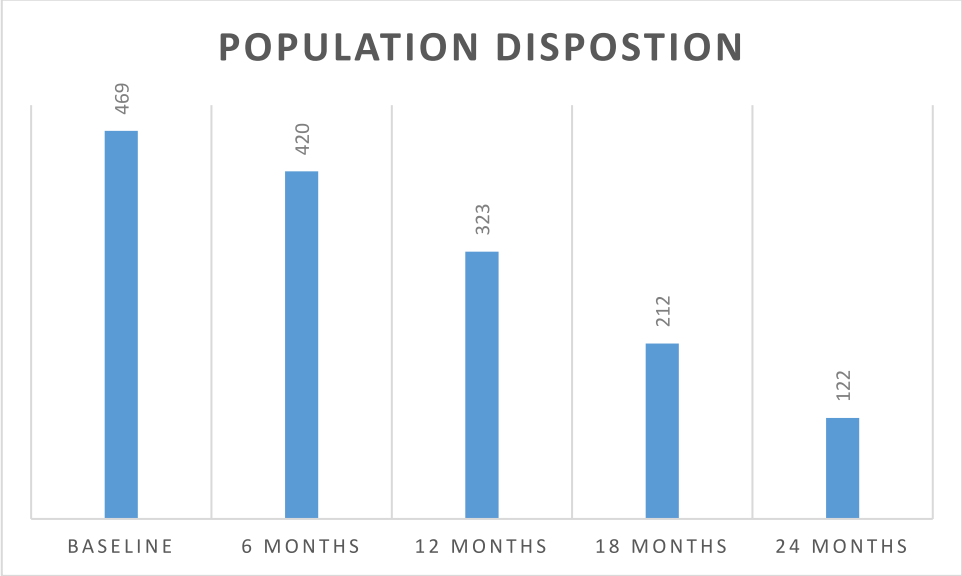

Fig. 1. Patient disposition (patients who continued evolocumab therapy over the follow-up periods).

Table 2
Safety outcomes.

Outcomes	Follow-up			
	6-month	12-month	18-month	24-month
Myocardial infarction	31.53 (15.21—65.36)	31.95 (18.72—54.55)	27.81 (16.88—45.81)	24.19 (14.67—39.88)
Unstable angina requiring hospitalization	31.49 (15.19 – 65.28)	27.76 (15.50—49.72)	22.21 (12.69—38.87)	19.39 (11.07—33.96)
Coronary revascularization	63.20 (38.06—104.94)	57.59 (38.73—85.63)	45.00 (30.44—66.54)	44.21 (30.57—63.93)
Stroke	8.87 (2.23—35.20)	9.86 (3.71—26.14)	11.05 (4.98—24.49)	12.84 (6.45—25.57)
Transient ischemic attack	4.46 (0.63—31.54)	2.45 (0.34—17.39)	1.83 (0.25—12.97)	1.59 (0.22—11.29)
Heart failure requiring hospitalization	26.94 (12.23—59.32)	17.31 (8.30—36.08)	18.47 (9.99—34.14)	17.74 (9.88—31.87)
Rhabdomyolysis with renal dysfunction	4.46 (0.63—31.54)	4.91 (1.23—19.58)	3.66 (0.91—14.61)	3.18 (0.79—12.72)
Rhabdomyolysis without renal dysfunction	8.93 (2.24—35.49)	4.91 (1.23—19.60)	3.66 (0.92—14.63)	3.19 (0.80—12.73)
Myalgia	44.96 (24.53—82.40)	29.87 (17.11—52.16)	22.32 (12.75—39.06)	22.68 (13.51—38.07)

Numbers represent the cumulative incidence rate per 1000 person-years (with 95%CI).

general the incidence rate per 1000 person-years decreases over follow-up periods from 6 months to 24 months. The ranges (minimum, maximum) of the incidence rates of the most frequent adverse events of interest in chronological order were: coronary revascularization (44.21 to 63.2), myalgia (22.32 to 44.96), myocardial infarction (24.19 to 31.53), unstable angina requiring hospitalization (19.39 to 31.49), heart failure requiring hospitalization (17.31 to 26.94) and transient ischemic attack (1.59 to 4.46). Although the incidence of rhabdomyolysis without renal dysfunction was higher than that of rhabdomyolysis with renal dysfunction at 6 months follow-up (8.93 vs. 4.46 per 1000 person-years), the incidence of rhabdomyolysis with or without renal dysfunction became similar at 12, 18, and 24 months follow-up. At 24 and 6 months of follow-up, the incidence of transient ischemic attack ranged from 1.59 to 4.46 per 1000 person-years, respectively. The incidence of stroke rises with the length of follow-up, from 8.87 to 12.84 per 1000 person-years at 6 and 24 months follow-ups, respectively. Table 3 summarizes the cumulative incidence throughout the study period and the time to event. Coronary revascularization was the most common incident event (5.8 %) in 27 patients, while transient ischemic attack (0.2 %) happened in one patient. Patients who developed rhabdomyolysis without renal dysfunction had the shortest average time to incidence (148 days). Patients who experienced a stroke had the longest mean time to event (387. 5 days).

Table 3
Cumulative incidence of adverse events and time to event (mean (sd), and median (range)).

Outcomes	Cumulative incidence N (%)	Mean time to event, (SD) Days	Median time to event, (Range) Days
Myocardial infarction	**15 (3.2)**	**207.9, (135.8)**	**224 (31, 489)**
Unstable angina requiring hospitalization	**12 (2.6)**	**187.8 (125.6)**	**146.5 (32, 468)**
Coronary revascularization	**27 (5.8)**	**223.7 (183)**	**180 (10, 715)**
Stroke	**8 (1.7)**	**387.5 (254)**	**343 (41, 694)**
Transient ischemic attack	**1 (0.2)**	**161**	**161**
Heart failure requiring hospitalization	**11 (2.3)**	**242.6 (205)**	**162 (33, 551)**
Rhabdomyolysis with renal dysfunction	**2 (0.4)**	**228.5 (95.5)**	**228.5 (161, 296)**
Rhabdomyolysis without renal dysfunction	**2 (0.4)**	**148 (21.2)**	**148 (131, 161)**
Myalgia	**14 (3.0)**	**211.9 (187.2)**	**139 (41, 636)**

SD: Standard Deviation

3.3. *Effectiveness outcomes*

Evolocumab use was associated with significant reductions from baseline in the mean LDL (−1.17, −1.4, −1.51 and −1.31 mmol/L; *p*-

value < 0.001), and total cholesterol (−1.78, −1.58, −1.48, and −1.07 mmol/L; *p*-value < 0.001) at the 6, 12, 18, and 24 months follow-ups, respectively (Table 3). However, evolocumab had no statistically significant effect on HDL or triglycerides (Table 4).

4. Discussion

The present analysis examined the real-world data on safety, and effectiveness of evolocumab in Saudi Arabia. A total of 469 patients with either familial hypercholesterolemia (FH) or mixed dyslipidemia were started on evolocumab and were followed for up to 24-months. Throughout the study period, evolocumab significantly reduced LDL and total cholesterol levels without causing any significant safety concerns.

Treatment with evolocumab resulted in a reduction of LDL levels by approximately 1.35 mmol/L throughout all the follow up periods. This translates to an average of 28.9 % decrease in LDL levels. The percentage in reduction reported from our observation differ from previous studies in which LDL lowering ranged between 55–60 %.(Koskinas et al., 2019; Sabatine et al., 2017; Toth et al., 2018) The lower percentage proclaimed can be further explained by the following: firstly, changes in background lipid lowering therapy for instance physicians changed the high intensity statin to a moderate intensity statin when co-administration with evolocumab; secondly, there was a shortage in medication supply during the study period in which therapy was interrupted. In addition, adherence to the medication was not known due to the lack of documentation. Lastly, it could be attributed to small sample size effect as not all patients who were included in the analysis had laboratory testing throughout the follow-up period, thus the findings do not reflect the whole study population.

Most of the statin trials concluded a 31 % reduction in ASCVD when achieving LDL goals < 1.8 mmol/l, this means that 69 % of the risk for ASCVD still exist. However, when combining statin with PSCK9 inhibitors an additional 25–35 % LDL lowering can be achieved thus mitigate to the intrinsic counterbalancing effect of statins when given in combination which reflects to further decrease in CVD without further increase in the risk of stroke. In the FOURIER landmark cardiovascular trial evolocumab resulted in the reduction myocardial infarction (MI) (HR 0.73; 95 %CI 0.65–0.82) and stroke (HR 0.79, 95 %CI 0.66–0.95). (Sabatine et al., 2017) In our study coronary artery disease was the most common comorbidity.

Lipid testing plays a crucial role as it aids in assessing adherence to medication and the need for further intensification of lipid therapy. Similar to the study conducted by Gupta et al. and Al Faraidy et al. we report a suboptimal LDL testing after therapy initiation or escalation. As only 15 % of our patients had a lipid panel at 6 month following therapy and 18 % were tested during their annual visit. (Al Faraidy et al., 2023; Gupta et al., 2022) The percentage of patients undergoing lipid panel testing decreases to 12 % and 6 % at 18 month and 24 months, respectively. This could be due to clinicians forgetting to re-order LDL-C lab values in clinical practice settings after therapy initiation or modification thus, further reflects in the number of patients achieving their LDL goals. Such findings highlight the need for guidance when implementing therapy to have laboratory monitoring throughout the therapeutic course, especially in high risk patients to further identify patients of need for further modification or intensification.

The safety and effectiveness of using evolocumab in patients with hyperlipidemias were assessed in a number of real-world studies. (Barrios et al., 2020; Eloso et al., 2023; Gayoso-Rey et al., 2021; Giugliano et al., 2017; Nanchen et al., 2022; Zhang et al., 2023) These studies revealed favorable effectiveness with no significant adverse events. Overall, our results were in line with earlier research, and we were able to assess the effectiveness and safety of using evolocumab for 6 to 24 months. Our results demonstrate favorable effectiveness of evolocumab in situations where statins alone are insufficient to achieve the desired LDL level. Additionally, our study offered safety insights into the most significant adverse events of concern during a 24-month period of evolocumab use. Future studies especially in Saudi Arabia exploring the effectiveness and safety of evolocumab by including more adverse events over longer periods of time, with larger sample sizes, and individuals with complex and coexisting chronic conditions may benefit from these findings.

Compared to other real-world data, we had a large sample size. However, our study has some limitations that needs to be acknowledged, first the retrospective nature of the study might introduce some documentation bias due to the complexity of the chart review process. Second, the lack of neurocognitive adverse event's assessment as well as not including other adverse events. In addition, a small amount of data collection occurred during the COVID-19 pandemic, which may have affected access and availability of laboratory testing. Also, the inconsistency in how often laboratories request lipid profiles has resulted in a reduced sample size for assessing effectiveness. Lastly, the assessment of adherence and side effects were based on notes documented on patients' file.

5. Conclusion

This study's findings are consistent with pivotal studies and real-world data. With a reasonable safety profile, evolocumab is an effective therapeutic option for decreasing LDL levels in patients with mixed dyslipidemia and primary hypercholesterolemia. When statins alone are insufficient, evolocumab may help reduce LDL levels to therapeutic

Table 4
Effectiveness outcomes.

Follow-up	Outcome	N	Baseline (mean ± SD)	At follow –up (mean ± SD)	Difference	
					mean (95 %CI)	*p*-value
6 months	LDL	73	4.65 ± 2.60	3.48 ± 3.43	−1.17 (−1.66, −0.68)	**<0.001**
	Total Cholesterol	76	6.49 ± 2.71	4.71 ± 2.87	−1.78 (−2.26, −1.30)	**<0.001**
	HDL	73	1.11 ± 0.32	1.07 ± 0.29	−0.04 (−0.10, 0.02)	0.18
	Triglycerides	71	2.52 ± 3.90	1.76 ± 0.98	−0.76 (−1.67, 0.16)	0.11
12 months	LDL	87	4.64 ± 2.82	3.24 ± 3.42	−1.4 (−1.76, −1.04)	**<0.001**
	Total Cholesterol	89	6.46 ± 3.07	4.88 ± 3.44	−1.58 (−1.96, −1.19)	**<0.001**
	HDL	87	1.06 ± 0.22	1.09 ± 0.31	0.03 (−0.03, 0.08)	0.36
	Triglycerides	79	1.80 ± 1.32	1.55 ± 0.96	−0.25 (−0.51, 0.01)	0.06
18 months	LDL	60	4.40 ± 3.08	2.89 ± 2.88	−1.51 (−1.98, −1.05)	**<0.001**
	Total Cholesterol	60	6.01 ± 3.05	4.53 ± 2.69	−1.48 (−2.00, −0.97)	**<0.001**
	HDL	60	1.06 ± 0.25	1.33 ± 1.88	0.27 (−0.23, 0.76)	0.28
	Triglycerides	54	1.84 ± 1.25	1.66 ± 0.97	−0.18 (−0.47, 0.12)	0.24
24 months	LDL	31	5.21 ± 3.49	3.90 ± 3.63	−1.31 (−1.98, −0.64)	**<0.001**
	Total Cholesterol	31	6.76 ± 3.54	5.69 ± 3.53	−1.07 (−1.81, −0.32)	**0.01**
	HDL	31	0.98 ± 0.23	1.03 ± 0.24	0.05 (−0.01, 0.11)	0.09
	Triglycerides	30	1.84 ± 0.93	1.93 ± 1.48	0.09 (−0.29, 0.49)	0.61

levels in real-world clinical practice.

CRediT authorship contribution statement

Abdulaali R. Almutairi: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Walaa A. Alshahrani:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Ghaida K. Alhathlol:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Fatimah Alsheikh:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Abdulaziz Alakeel:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Majed S. Al Yami:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Mohammad Fouda:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Omar A. Almohammed:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Meshal S. Alhamed:** Writing – review & editing, Validation, Resources, Methodology, Data curation, Conceptualization. **Awatif Hafiz:** Writing – review & editing, Resources, Methodology, Data curation. **Hussam Kutbi:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization. **Alaa Bagalagel:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization. **Aisha Alharbi:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Mashael Alaboud:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization. **Sarah Aljohani:** Writing – review & editing, Resources, Data curation, Conceptualization. **Waddah Ashram:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Al Faraidy, K., Akbar, M., Shehri, M., Aljarallah, M., Abdin Hussein, G., Dashti, R., Al Qudaimi, A., Al Nouri, F., Awan, Z., Essam, A., 2023. Multizonal observational study conducted by clinical practitioners on evolocumab use in subjects with hyperlipidemia in Saudi Arabia and Kuwait: Results from the ZERBINI study. PLoS One 18, e0278821.

Al Sifri, S.N., Almahmeed, W., Azar, S., Okkeh, O., Bramlage, P., Jünger, C., Halawa, I., Ambegaonkar, B., Wajih, S., Brudi, P., 2014. Results of the Dyslipidemia International Study (DYSIS)-Middle East: clinical perspective on the prevalence and characteristics of lipid abnormalities in the setting of chronic statin treatment. PLoS One 9, e84350.

Allen, J.M., Arnold, S.V., Lohr, N.L., Reisman, L., Ghannam, A.F., Sanganalmath, S.K., Khan, I., Iorga, S., Kumbhani, D., 2019. assessing low-density lipoprotein cholesterol risk in secondary prevention patients within the PINNACLE national outpatient registry. Circulation 140, A12904–A. https://www.ahajournals.org/doi/abs/10.1161/circ.140.suppl_1.12904?af=R.

Balling, M., Nordestgaard, B.G., Langsted, A., Varbo, A., Kamstrup, P.R., Afzal, S., 2020. Small dense low density lipoprotein cholesterol predicts atherosclerotic cardiovascular disease in the Copenhagen General Population Study. J. Am. Coll. Cardiol. 75, 2873–2875. https://doi.org/10.1016/j.jacc.2020.03.072.

Barrios, V., Escobar, C., Arrarte, V., García, E., Fernández, M.R., Rincón, L.M., Roldán, C., 2020. First national registry on the effectiveness and safety of evolocumab in clinical practice in patients attended in cardiology in Spain. The RETOSS-CARDIO study. Clínica e Investig. En Arterioscler. (english Ed. 32, 231–241. https://doi.org/10.1016/j.arteri.2020.05.002.

Blais, J.E., Wei, Y., Knapp, M., Wong, I., Wei, L., Chan, E.W., 2022. Trends in PCSK9 Inhibitor Utilization in the United States, Europe and Other Countries: An Analysis of International Sales Data. Am. Heart J. 248, 13–20. https://doi.org/10.1016/j.ahj.2022.02.008.

Eloso, J., Awad, A., Zhao, X., Cunningham, F.E., Zhang, R., Dong, D., Kelley, C., Glassman, P.A., Aspinall, S.L., 2023. PCSK9 Inhibitor Use and Outcomes Using Concomitant Lipid-Lowering Therapies in the Veterans Health Administration. Am. J. Med. Open 9, 100035. https://doi.org/10.1016/j.ajmo.2023.100035.

Gayoso-Rey, M., Díaz-Trastoy, O., Romero-Ventosa, E.Y., García-Beloso, N., González-Freire, L., Lorenzo-Lorenzo, K., Mantiñán-Gil, B., Palmeiro-Carballeira, R., Bravo-Amaro, M., del Mar López-Gil-Otero, M., 2021. Effectiveness, safety, and adherence to treatment of proprotein convertase subtilisin/Kexin type 9 inhibitors in real practice. Clin. Ther. 43, e111–e121. https://doi.org/10.1016/j.clinthera.2021.02.002.

Ginsberg, H.N., Rader, D.J., Raal, F.J., Guyton, J.R., Baccara-Dinet, M.T., Lorenzato, C., Pordy, R., Stroes, E., 2016. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. Cardiovasc. Drugs Ther. 30, 473–483. https://doi.org/10.1007/s10557-016-6685-y.

Gitt, A.K., Lautsch, D., Ferrières, J., De Ferrari, G.M., Vyas, A., Baxter, C.A., Bash, L.D., Ashton, V., Horack, M., Almahmeed, W., 2017. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: results from the Dyslipidemia International Study II. Atherosclerosis 266, 158–166. https://doi.org/10.1016/j.atherosclerosis.2017.08.013.

Giugliano, R.P., Pedersen, T.R., Park, J.-G., De Ferrari, G.M., Gaciong, Z.A., Ceska, R., Toth, K., Gouni-Berthold, I., Lopez-Miranda, J., Schiele, F., 2017. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet 390, 1962–1971. https://doi.org/10.1016/S0140-6736(17)32290-0.

Grundy, S.M., Stone, N.J., Bailey, A.L., Beam, C., Birtcher, K.K., Blumenthal, R.S., Braun, L.T., De Ferranti, S., Faiella-Tommasino, J., Forman, D.E., 2019. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 139, e1082–e1143. https://doi.org/10.1161/CIR.0000000000000625.

Gupta, M., Mancini, G.B.J., Wani, R.J., Ahooja, V., Bergeron, J., Manjoo, P., Pandey, A.S., Reiner, M., Beltran, J., Oliveira, T., 2022. Real-world insights into evolocumab use in patients with hyperlipidemia: Canadian analysis from the ZERBINI study. CJC Open 4, 558–567. https://doi.org/10.1016/j.cjco.2022.03.003.

Hovingh, G.K., Raal, F.J., Dent, R., Stefanutti, C., Descamps, O., Masana, L., Lira, A., Bridges, I., Coll, B., Sullivan, D., 2017. Long-term safety, tolerability, and efficacy of evolocumab in patients with heterozygous familial hypercholesterolemia. J. Clin. Lipidol. 11, 1448–1457. https://doi.org/10.1016/j.jacl.2017.09.003.

Karatasakis, A., Danek, B.A., Karacsonyi, J., Rangan, B.V., Roesle, M.K., Knickelbine, T., Miedema, M.D., Khalili, H., Ahmad, Z., Abdullah, S., 2017. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. J. Am. Heart Assoc. 6, e006910.

Karr, S., 2017. Epidemiology and management of hyperlipidemia. Am. J. Manag. Care 23, S139–S148. https://www.ajmc.com/view/epidemiology-and-management-of-hyperlipidemia-article.

Kastelein, J.J.P., Ginsberg, H.N., Langslet, G., Hovingh, G.K., Ceska, R., Dufour, R., Blom, D., Civeira, F., Krempf, M., Lorenzato, C., 2015. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur. Heart J. 36, 2996–3003. https://doi.org/10.1093/eurheartj/ehv370.

Koskinas, K.C., Windecker, S., Pedrazzini, G., Mueller, C., Cook, S., Matter, C.M., Muller, O., Häner, J., Gencer, B., Crljenica, C., 2019. Evolocumab for early reduction of LDL cholesterol levels in patients with acute coronary syndromes (EVOPACS). J. Am. Coll. Cardiol. 74, 2452–2462. https://doi.org/10.1016/j.jacc.2019.08.010.

Mach, F., Baigent, C., Catapano, A.L., Koskinas, K.C., Casula, M., Badimon, L., Chapman, M.J., De Backer, G.G., Delgado, V., Ference, B.A., 2020. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur. Heart J. 41, 111–188. https://doi.org/10.1093/eurheartj/ehz455.

Nanchen, D., Carballo, D., Bilz, S., Rickli, H., Koskinas, K.C., Mach, F., Mueller, C., Crljenica, C., Rossi, M., Reichert, N., 2022. Effectiveness, adherence, and safety of evolocumab in a swiss multicenter prospective observational study. Adv. Ther. 39, 504–517. https://doi.org/10.1007/s12325-021-01962-w.

Pearson, G.J., Thanassoulis, G., Anderson, T.J., Barry, A.R., Couture, P., Dayan, N., Francis, G.A., Genest, J., Gregoire, J., Grover, S.A., 2021. Society Guidelines 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can. J. Cardiol. 37, 1129–1150. https://doi.org/10.1016/j.cjca.2021.03.016.

Raal, F.J., Stein, E.A., Dufour, R., Turner, T., Civeira, F., Burgess, L., Langslet, G., Scott, R., Olsson, A.G., Sullivan, D., 2015. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 385, 331–340. https://doi.org/10.1016/S0140-6736(14)61399-4.

Roth, E.M., Davidson, M.H., 2018. PCSK9 Inhibitors: Mechanism of Action, Efficacy, and Safety. Rev. Cardiovasc. Med. 19 (S1), 31–46. https://doi.org/10.3909/ricm19S1S0002.

Sabatine, M.S., Giugliano, R.P., Keech, A.C., Honarpour, N., Wiviott, S.D., Murphy, S.A., Kuder, J.F., Wang, H., Liu, T., Wasserman, S.M., 2017. Evolocumab and clinical outcomes in patients with cardiovascular disease. N. Engl. J. Med. 376, 1713–1722. https://www.nejm.org/doi/10.1056/NEJMoa1615664.

Su, L., Mittal, R., Ramgobin, D., Jain, R., Jain, R., 2021. Current management guidelines on hyperlipidemia: the silent killer. J. Lipids 2021. https://doi.org/10.1155/2021/9883352.

Toth, P.P., Sattar, N., Blom, D.J., Martin, S.S., Jones, S.R., Monsalvo, M.L., Elliott, M., Davis, M., Somaratne, R., Preiss, D., 2018. Effect of evolocumab on lipoprotein particles. Am. J. Cardiol. 121, 308–314. https://doi.org/10.1016/j.amjcard.2017.10.028.

Trinder, M., Francis, G.A., Brunham, L.R., 2020. Association of monogenic vs polygenic hypercholesterolemia with risk of atherosclerotic cardiovascular disease. JAMA Cardiol. 5, 390–399. https://10.1001/jamacardio.2019.5954.

Zhang, T., Zhang, Y., Yang, Y., Liao, H., Li, X., Liu, R., Liu, X., Yang, L., Yue, W., 2023. Real-world effectiveness and safety of evolocumab in very high-risk atherosclerotic cardiovascular disease patients with acute ischemic stroke. J. Thromb. Thrombolysis 1–10. https://doi.org/10.1007/s11239-023-02925-4.