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REVIEW

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A mini-review of efficacy, safety, and influence of novel evinacumab on familial hypercholesterolemia

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Abstract

Background Familial hypercholesterolemia (FH) poses a substantial risk of cardiovascular diseases. The recent approval of evinacumab signifies a breakthrough in FH management. This review synthesizes evidence from diverse clinical trials, examining evinacumab's efficacy, safety, and broader impact on hypercholesterolemia.

Body As highlighted by multiple trials, Evinacumab demonstrates robust efficacy in reducing LDL-C levels, particularly in refractory cases. Its sustained impact, evidenced by enduring reductions in LDL-C levels throughout extended treatment periods, positions it as a potential long-term solution. While the safety profile appears favorable, instances of deaths underline the importance of holistic clinical management and ongoing surveillance. The clinical implications are profound, suggesting evinacumab's potential inclusion in guidelines for managing severe lipid disorders.

Conclusion Future research directions emphasize inclusivity, diversity, and real-world applications to establish sustained efficacy and safety across diverse populations. Integrating evinacumab into clinical guidelines requires evidence-based recommendations, necessitating collaboration between researchers, clinicians, and guideline developers.

Keywords Familial Hypercholesterolemia, Evinacumab, Cholesterol

Introduction

Familial hypercholesterolemia (FH), a prevalent genetic disorder with an autosomal dominant pattern of inheritance, is characterized by markedly elevated blood low-density lipoprotein cholesterol (LDL-C) levels surpassing the normative threshold [1, 2]. FH patients exhibit distinctive lipid profiles, including heightened cholesterol levels, normal or diminished high-density lipoprotein (HDL), and often normal triglyceride (TG) levels, alongside an increased amount of LDL-C [3]. The clinical presentation of FH varies between heterozygous (HeFH) and homozygous (HoFH) forms, each posing unique challenges in diagnosis and management [4, 5]. Despite advances in therapeutic options, FH patients remain at an elevated risk of cardiovascular diseases, particularly coronary artery disease (CAD) [3]. Recognizing the significant impact of modifiable risk factors such as nutrition, exercise, and lifestyle, the management of FH necessitates a dual focus on maintaining a healthy routine and promptly initiating aggressive hypolipidemic medication [6].

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In this context, the recent approval of evinacumab by the European Union in February 2021 marks a milestone in hypercholesterolemia management [7]. Regeneron Pharmaceuticals developed evinacumab, an IgG4 monoclonal antibody targeting angiopoietin-like 3 protein (ANGPTL3) [8, 9]. Inhibiting ANGPTL3 unleashes the action of lipoprotein lipase (LPL) and endothelial lipase (EL), critical enzymes in lipid metabolism [10]. Utilizing genetically engineered recombinant Chinese hamster ovary cells, this humanized IgG4 anti-ANGPTL3 monoclonal antibody boasts two disulfide-linked human heavy chains and human kappa light chains, each with 453 and 214 amino acid residues, respectively [11]. Evinacumab stands out as a promising therapeutic agent, employing a unique mechanism of action targeting angiopoietin-like 3 (ANGPTL-3) protein [12]. Evinacumab operates as a human monoclonal antibody specifically designed to interfere with the inhibitory effect of ANGPTL-3 on lipoprotein lipase (LPL), thereby enhancing lipid clearance and reducing circulating low-density lipoprotein (LDL) cholesterol levels [13].

ANGPTL3, a vascular endothelial growth factors (VEGF) family component primarily expressed in the liver, regulates lipid metabolism by inhibiting endothelial lipase and lipoprotein lipase activities [12, 13]. Loss-of-function variants in the ANGPTL3 gene are associated with reduced LDL cholesterol levels, emphasizing its significance as a therapeutic target [14]. Evinacumab's multifaceted action begins by reducing ANGPTL3 activity, unleashing lipase activities, and facilitating lipoprotein hydrolysis, decreasing triglyceride (TG) levels [15, 16]. Forming an immune complex with evinacumab inhibits ANGPTL3, enhancing the removal of very low-density lipoprotein (VLDL) remnants and ultimately reducing LDL cholesterol levels via a mechanism independent of LDL receptors [10, 17]. This mechanism of action contrasts with other emerging strategies in cardiovascular medicine. For instance, gene silencing techniques utilizing antisense nucleotides to target ANGPTL-3 mRNA represent an innovative approach to modulating lipid metabolism at the genetic level. Additionally, the inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has garnered significant attention, with monoclonal antibodies such as evolocumab and alirocumab demonstrating efficacy in lowering LDL cholesterol levels by preventing PCSK9-mediated degradation of LDL receptors [14] (Fig. 1).

While initial studies have demonstrated its efficacy in reducing LDL-C levels, the literature still needs to analyze its long-term impact and safety profile [11, 12]. Moreover, existing treatments may have limitations, including adherence issues, side effects, and variable responses among diverse patient populations. This review examines the efficacy, safety, and influence of novel evinacumab on FH. Understanding the long-term efficacy, safety profile, and broader impact of evinacumab on hypercholesterolemia is crucial for informing clinical decision-making and refining treatment strategies.

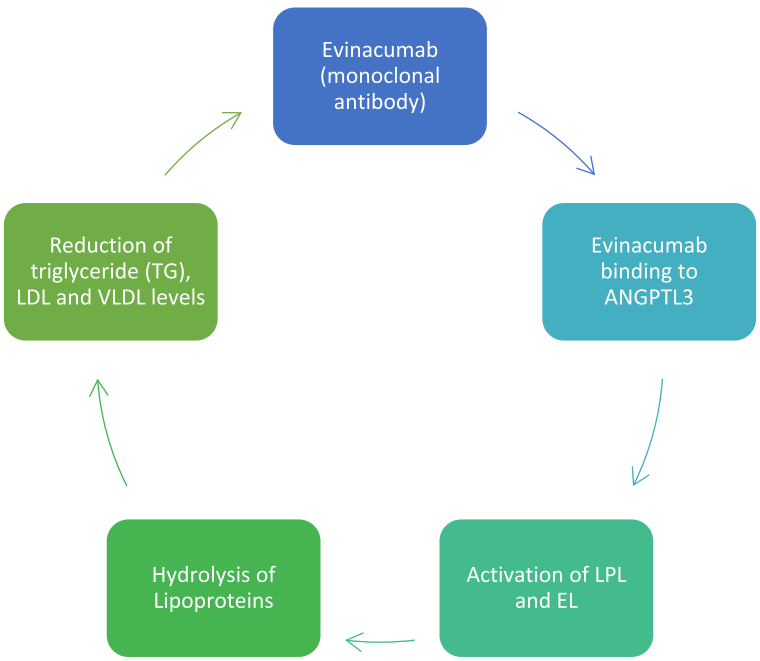

Fig. 1 Mechanism of action of evinacumab

Methodology

To ensure a comprehensive review, relevant literature was searched. Electronic databases, including PubMed, MEDLINE, Embase, and Cochrane Library, were searched (see Table 1). The search terms included "evinacumab," "hypercholesterolemia," "LDL cholesterol," "safety," and "efficacy." Additionally, manual searches of key journals and references from relevant articles were performed to identify additional studies.

Studies were included if they met the following criteria:

- Published in English.
- Examined the efficacy and safety of evinacumab in familial hypercholesterolemia.
- Involved human subjects.
- Provided relevant data on LDL cholesterol levels, cardiovascular outcomes, and safety profiles.

Studies were excluded if they were:

- Case reports, reviews, or conference proceedings.
- Studies with insufficient data on the outcomes of interest.

Data extraction was performed independently by two reviewers to ensure accuracy. Extracted information included study design, participant characteristics, intervention details, outcomes (including changes in LDL cholesterol levels, cardiovascular events, and adverse events), and follow-up duration.

A narrative synthesis approach was employed to summarise the findings due to the anticipated heterogeneity in study designs and outcomes. Key themes related to evinacumab's long-term efficacy, safety, and influence on hypercholesterolemia were identified and presented.

Current evidence on efficacy and safety

A. Overview of efficacy

The efficacy of evinacumab has been studied across various clinical trials (see Table 2). In a pivotal clinical trial by Raal et al. (2023), 64 patients completing a 24-week intravenous evinacumab treatment exhibited a remarkable – 49.6% reduction in total LDL-P compared to -5.1% with the placebo [18]. The study design included two distinct periods to evaluate the efficacy and safety profile of Evinacumab, namely a double-blind treatment period of 24 weeks followed by an open-label treatment period for another 24 weeks. The LDL-C data from 58 patients showed a substantial mean reduction of 46.3% from baseline to week 48 with open-label evinacumab. Notably, in the double-blind treatment period the placebo arm showed more mean percent reduction in LDL-P by 55.8% compared to a 42.7% reduction in the evinacumab arm, underscoring the efficacy of evinacumab in LDL-P reduction [18]. The trial further elucidated the impact of evinacumab on diverse lipid profiles. In the overall population, there were significant reductions in HDL-C (mean, 0.4%), non-HDL-C (mean, 48.9%), total cholesterol (mean, 47.0%), ApoB (mean, 40.8%), triglycerides (median, 51.9%), and Lp(a) (median, 16.3%) from baseline to 48 weeks. Interestingly, the mean percentage

Table 1 Methodology

Methodology	Details
Literature Search	- Conducted a search of relevant literature to ensure a comprehensive review
	- Electronic databases searched: PubMed, MEDLINE, Embase, Cochrane Library. See Table 1 for details
	- Search terms included: "evinacumab," "hypercholesterolemia," "LDL cholesterol," "safety," and "efficacy."
	- Manual searches of key journals and references from relevant articles were performed to identify additional studies
Inclusion criteria for studies	- Published in English
	- Examined the efficacy and safety of evinacumab in familial hypercholesterolemia
	- Involved human subjects
	- Provided relevant data on LDL cholesterol levels, cardiovascular outcomes, and safety profiles
Exclusion criteria for studies	- Case reports, case series, reviews, or conference proceedings
	- Studies with insufficient data on the outcomes of interest
Data extraction	- Independently performed by two reviewers to ensure accuracy
	- Extracted information included study design, participant characteristics, intervention details, outcomes (LDL cholesterol levels, cardiovascular events, adverse events), and follow-up duration
Synthesis and presentation	- Narrative synthesis approach employed to summarize findings due to anticipated heterogeneity in study designs and outcomes
	- Key themes related to evinacumab's long-term efficacy, safety, and influence on hypercholesterolemia identified and presented

Table 2 Study characteristics

Author and year	Study design	Sample size	Positive outcome	Negative
Robert S Rosenson, et al. (2023)	Randomized clinical trial	96	A total of 96 patients; 52 female [54.2%]) entered the OLTP, of whom 88 (91.7%) completed the Open-Label Treatment Plan. Mean (SD) baseline LDL-C level was 145.9 (55.2) mg/dL. At week 72, evinacumab, 15 mg/kg, reduced mean (SD) LDL-C level from baseline by 45.5% (28.7%) in the overall cohort. Evinacumab, 15 mg/kg, reduced mean (SD) apolipoprotein B (38.0% [22.1%]), non-high-density lipoprotein cholesterol (48.4% [23.2%]), total cholesterol (42.6% [17.5%]), and median (IQR) fasting triglyceride (57.2% [65.4–44.4%]) levels at week 72 from baseline in the overall cohort. Treatment-emergent adverse events occurred in 78 of 96 patients (81.3%). Serious treatment-emergent adverse events occurred in 9 of 96 patients (9.4%); all were considered unrelated to study treatment	Treatment Emergent Adverse effects (TEAEs) occurred in 78 of 96 patients (81.3%). Serious TEAEs occurred in 9 of 96 patients (9.4%); all were considered unrelated to study treatment The most common TEAE with evinacumab, 15 mg/kg, given intravenously Q4W was nasopharyngitis (12.5% [12 of 96] Four of 96 patients (4.2%) presented with laboratory abnormalities pertaining to liver function, one of whom had TEAEs of increased alanine aminotransferase and increased aspartate aminotransferase that resolved completely and were considered unrelated to study treatment by the investigator Four of 96 patients (4.2%) experienced at least 1 TEAE considered related to study treatment by the investigator; these were an increase in LDL-C level of moderate severity ($n=1$), soft feces and frequent bowel movements of mild severity ($n=1$), malaise (considered an infusion-related reaction; $n=1$), and influenzalike illness of mild severity ($n=1$). In all 4 patients, there was complete resolution of TEAEs, and no changes to study treatment were made Serious TEAEs occurred in 9 of 96 patients (9.4%); these were carotid artery stenosis ($n=1$), chest pain ($n=1$), coronavirus infection ($n=1$), gallbladder polyp ($n=1$), gastrointestinal motility disorder ($n=1$), joint effusion ($n=1$), pulmonary embolism ($n=1$), atrial fibrillation and transitional cell carcinoma (both in a single patient), and atrial fibrillation, palpitations, and dyspnea (all in a single patient). These serious TEAEs were not considered drug-related by the investigator. No deaths or TEAEs leading to discontinuation were reported

Table 2 (continued)

Author and year	Study design	Sample size	Positive outcome	Negative
Rosenson, Raal, et al (2023)	A randomized, double-blind, placebo-controlled, parallel-group study	57	patients in the evinacumab group had a relative reduction from baseline in the LDL cholesterol level of 47.1%, as compared with an increase of 1.9% in the placebo group, for a between-group least-squares mean difference of − 49.0 percentage points (95% confidence interval [CI], − 65.0 to − 33.1; $P < 0.001$)	Adverse events during the treatment period occurred in 66% of the patients in the evinacumab group and in 81% of those in the placebo group They included Nasopharyngitis, Influenza-like illness, headache, rhinorrhea, etc The Serious adverse events during the treatment period occurred in 2 patients (5%) in the evinacumab group and were reported as urosepsis and a suicide attempt An increase in the level of either alanine or aspartate aminotransferase was reported in 2 of 44 patients (5%) in the evinacumab group and in 2 of 21 patients (10%) in the placebo group, increases that were less than 3 times and 5 times the upper limit of the normal range, respectively
Frederick J. Raal et al. (2023)	Double-blind trial	64	A total of 64 patients completed the Double Blind Treatment Period and received open-label evinacumab. Despite multiple lipid lowering therapies, the mean baseline LDL-C at DBTP entry was 250.5 ± 162.3 mg/dL. From baseline to week 48 (end of Open-Label Treatement Period), evinacumab reduced mean LDL-C by 46.3% (mean reduction, 134.3 ± 117.3 mg/dL), with similar mean LDL-C reductions for patients with null-null (47.2%) and non-null variants (45.9%)	Adverse events occurred in 47 (73.4%) patients; 4 (6.3%) patients experienced adverse events considered evinacumab-related (drug hypersensitivity, infusion-related reaction and asthenia, generalized pruritis, and muscle spasms)
Mariko Harada-Shiba (2023)	Randomized clinical trial	96	The safety profile of evinacumab (IV and SC) in both ethnicities was comparable with placebo, with no serious or severe treatment-emergent adverse events. Pharmacokinetic profiles were comparable between Japanese and Caucasian subjects across IV and SC groups. Mean calculated LDL-C decreased from baseline with both IV doses, beginning on day 3 up to week 8. Triglyceride changes observed with evinacumab IV were rapid (seen by day 2) and sustained up to week 8. Evinacumab SC doses also reduced LDL-C and triglyceride levels, although lower doses induced smaller changes. Evinacumab (IV and SC) reduced other lipids, including apolipoprotein B, versus placebo	TEAEs occurred in six (50.0%) subjects in the combined placebo IV treatment group and in 15 (41.7%) subjects in the combined evinacumab IV treatment groups, with similar rates between the two evinacumab IV dose groups Hypersensitivity AEs were reported at a higher frequency (27.8%) for evinacumab-treated subjects in the 300 mg QW group versus the 300 mg single-dose group Treatment-related TEAEs and injection-site reactions were reported by two (11.1%) and six (33.3%) subjects, respectively, only in the 300 mg QW group. No serious AEs (SAEs), severe TEAEs, TEAEs of special interest, TEAEs leading to study discontinuation, or TEAEs leading to death were observed in any SC or IV treatment groups

Table 2 (continued)

Author and year	Study design	Sample size	Positive outcome	Negative
Frederick J. Raal et al. (2021)	Randomized, double-blind, placebo-controlled study	25	Combination therapy with alirocumab and evinacumab reduced LDL-C by more than 60% in patients with HoFH and was well tolerated	Not stated
Reeskamp, Nurmohamed et al. (2021)	Two HoFH patients with null/null LDLR variants, who participated in the R1500-CL-1629 randomized clinical trial (NCT03399786) evaluating the LDL cholesterol-lowering effect of evinacumab (a human antibody directed against ANGPTL3; 15 mg/kg intravenously once monthly), were included in this study. Patients underwent coronary computed tomography angiography (CCTA) before randomization and after 6 months of treatment	2	profound plaque reduction was observed with CCTA after intensive lipid-lowering therapy with statins, ezetimibe, LDL apheresis, and evinacumab. This shows that atherosclerotic plaques possess the ability to regress at a young age, even in HoFH patients	Both patients did not experience any serious adverse events during treatment with evinacumab or placebo

Table 2 (continued)

Author and year	Study design	Sample size	Positive outcome	Negative
Ronsenson, Burgess et al. (2020)	Randomized, double-blind, placebo-controlled study, phase 2 trial	272	In patients with refractory hypercholesterolemia, the use of evinacumab significantly reduced the LDL cholesterol level, by more than 50% at the maximum dose	The incidence of serious adverse events during the treatment period ranged from 3 to 16% across trial groups. Adverse events that occurred in at least 5% of the patients who received subcutaneous evinacumab (any of the three regimens) and occurred more frequently with subcutaneous evinacumab than with subcutaneous placebo included urinary tract infection (11% vs. 8%), injection-site erythema (6% vs. 3%), arthralgia (5% vs. 3%), and myalgia (5% vs. 0%).Adverse events that occurred in at least 5% of the patients who received intravenous evinacumab (either of the two regimens) and occurred more frequently with intravenous evinacumab than with intravenous placebo included abdominal pain (6% vs. 0%), back pain (7% vs. 6%), dizziness (7% vs. 0%), fatigue (7% vs. 6%), pain in an arm or leg (7% vs. 6%), nausea (7% vs. 0%), and nasopharyngitis (12% vs. 6%) In patients who received subcutaneous or intravenous evinacumab, few high-grade adverse events were observed In the subcutaneous-treatment groups, the only adverse event resulting in treatment discontinuation that was considered by the investigator to be related to the trial drug was dyspnea, which occurred with subcutaneous evinacumab at a dose of 300 mg every 2 weeks and resolved fully Adverse events resulting in death occurred in one patient who was treated with subcutaneous evinacumab at a dose of 300 mg weekly (heart failure or cardiogenic shock) and one patient who was treated with subcutaneous evinacumab at a dose of 300 mg every 2 weeks (sudden cardiac death). These events occurred in patients with underlying heart disease and were not considered by the investigator to be related to the trial drug

Table 2 (continued)

Author and year	Study design	Sample size	Positive outcome	Negative
Frederick J et al. (2020)	double-blind, placebo-controlled, phase 3 trial	65	The mean baseline LDL cholesterol level in the two groups was 255.1 mg per deciliter, despite the receipt of maximum doses of background lipid-lowering therapy. At week 24, patients in the evinacumab group had a relative reduction from baseline in the LDL cholesterol level of 47.1%, as compared with an increase of 1.9% in the placebo group ($P < 0.001$); The LDL cholesterol level was lower in the evinacumab group than in the placebo group in patients with null–null variants (− 43.4% vs. + 16.2%) and in those with non-null variants (− 49.1% vs. − 3.8%) Patients in the evinacumab group had significantly lower levels of apolipoprotein B, non-HDL cholesterol, and total cholesterol from baseline to week 24 than those in the placebo group ($P < 0.001$ for all comparisons)	Adverse events during the treatment period occurred in 66% of the patients in the evinacumab group and in 81% of those in the placebo group (Table 3). No patients discontinued either evinacumab or placebo because of an adverse event; there were no deaths Serious adverse events during the treatment period occurred in 2 patients (5%) in the evinacumab group and were reported as urosepsis and a suicide attempt. Both patients recovered
Barnejee, Chan et al. (2019)	phase 2, proof-of-concept study	9	Overall mean peak reduction in LDL-C with evinacumab was − 58 ± 18%, occurring between week 4 and week 12, showing that ANGPTL3 inhibition substantially reduced LDL-C in all participants	Not Stated
Zahid Ahmad et al. (2019)	Randomized clinical trial	139	Dose-dependent reductions in triglycerides were observed in both studies, with a maximum reduction of 76.9% at day 3 with 10 mg/kg intravenously ($P < 0.0001$) in the single ascending dose study and of 83.1% at day 2 with 20 mg/kg intravenously once every 4 weeks ($P = 0.0003$) in the multiple ascending dose study. Significant reductions in other lipids were observed with most evinacumab doses versus placebo	No serious treatment-emergent adverse events or events leading to death or treatment discontinuation were reported. Elevations in alanine aminotransferase (7 [11.3%] SAD), aspartate aminotransferase (4 [6.5%] SAD), and creatinine phosphokinase (2 [3.2%) SAD, 1 [14.3%] MAD) were observed with evinacumab (none in the placebo groups), which were single elevations and were not dose-related
Gaudet, Gipe, et al. (2017)	a single-arm, open-label, proof-of-concept study	9	The preliminary results show a pronounced effect of evinacumab added to LLT in lowering LDL-C in HoFH patients, regardless of genotype	Most common drug-related events were injection-site reactions and hot flush

reductions for patients with or without apheresis were 43.8% and 47.6%, respectively, suggesting consistent efficacy across patient subgroups. Similarly, Reeskamp et al. (2021) evaluated Evinacumab's effect on two patients with null/null LDLR variants, showcasing promising results. Intravenous administration led to a significant reduction in pre-apheresis LDL cholesterol levels (2.48 ± 0.31 to 0.80 ± 0.16 mmol/l in patient A; 2.20 ± 0.13 to 0.78 ± 0.13 mmol/l in patient B) [19]. Follow-up CCTA revealed substantial regression in plaque burden, with patient A experiencing a 76% reduction and patient B an impressive 85% reduction in total plaque volume after 31.5 months, including 5 months of Evinacumab treatment. Reeskamp et al.'s study (2021) focuses uniquely on patients with null/null LDLR variants and utilizes CCTA for plaque assessment. While the study design adds novelty, the small sample size (two patients) raises concerns about statistical power. The absence of a control group limits the ability to attribute observed changes solely to evinacumab.

Banerjee et al. (2019) conducted a study assessing LDLR activity. Evinacumab, despite reducing LDL binding and uptake values, did not alter LDLR activity. This finding suggests that evinacumab's efficacy may be independent of direct LDLR functional improvement [20]. Gaudet et al.'s (2017) open-label study involving nine adults offers insights into real-world applications [21]. The multifaceted lipid profile assessment adds depth, but the small sample size and lack of a control group limit generalizability and causal inference. In the single-group, open-label study, evinacumab demonstrated significant efficacy in nine adults with HoFH. The treatment led to a 49% reduction in LDL cholesterol levels at week 4, with concurrent decreases in apolipoprotein B, non-HDL cholesterol, triglycerides, and HDL cholesterol.

Frederick et al. (2021) investigated the combination of alirocumab and evinacumab in 25 patients with FH, reporting substantial reductions in LDL-C (−62.9%), apolipoprotein B (−54.9%), and triglycerides (−54.5%) [22]. A study by Rosenson et al. (2023) demonstrated enduring reductions in LDL-C levels throughout 72 weeks with intravenous evinacumab [23]. It is noteworthy that Rosenson et al. 2023 explored the longer-term effects of Evinacumab in refractory hypercholesterolemic cases. A remarkable 45.5% reduction at the 72-week mark emphasizes its sustained efficacy, positioning evinacumab as a long-term solution for refractory hypercholesterolemia. Subcutaneous or intravenous administration of evinacumab in a trial involving 272 patients showcased promising longer-term efficacy. Subcutaneous administration led to a 10% reduction in LDL cholesterol levels at week 16 compared to placebo, while intravenous administration exhibited more than 25% reductions. Secondary efficacy analyses emphasised the consistency of evinacumab in lowering lipid levels, including a dose-dependent decrease in atherogenic lipoproteins and HDL cholesterol levels. A phase 3 trial by Raal et al. explored evinacumab's efficacy in 65 patients with homozygous familial hypercholesterolemia, demonstrating a significant 47.1% reduction in LDL cholesterol levels compared to a modest 1.9% increase in the placebo group at week 24. The substantial between-group difference of 49% underscores the robust efficacy of evinacumab in lowering LDL cholesterol, addressing a critical need in patients with severe hypercholesterolemia [24].

B. Safety parameters and adverse event management

In the clinical trial conducted by Raal et al. (2023), treatment-emergent adverse events (TEAEs) occurred in 73.4% of patients during the Open-Label Treatment Period (OLTP), with the most common TEAEs being nasopharyngitis (9.4%) and headache (9.4%). Reeskamp et al. (2021) reported no adverse reactions during their study, indicating a favorable safety profile [18]. Similarly, Banerjee et al. (2019) found that evinacumab was well-tolerated, with no treatment discontinuations due to adverse events [20]. Gaudet et al.'s (2017) study involving patients with HoFH reported that all participants experienced at least one adverse event, with back pain ($n=4$), nausea ($n=4$), and nasopharyngitis ($n=2$) being the predominant adverse events. Importantly, none of these events led to treatment discontinuation [22].

The safety of subcutaneous evinacumab was investigated in 266 patients in a study by Rosenson et al. (2021) [24]. Different doses and frequencies of administration were explored, and adverse events associated with intravenous administration of evinacumab were compared to those of a placebo group. Adverse events in the subcutaneous administration included diarrhea, headache, influenza-like illness, injection-site erythema, nausea, nasopharyngitis, and urinary tract infection, with varying occurrences based on different doses. Notably, the study by Mariko Harada-Shiba et al. (2021) involving healthy Japanese and Caucasian subjects revealed comparable profiles across different treatment groups [25]. However, there were slight variations between Japanese and Caucasian subjects in other dose groups. TEAEs were reported in 41.7% of subjects in the evinacumab group for the intravenous treatment groups, with similar rates across different IV dose groups. Hypersensitivity adverse events were experienced by a small percentage of subjects, with minimal differences between the placebo and evinacumab groups [23]. In the subcutaneous treatment groups, a higher incidence of TEAEs was observed in the evinacumab group compared to the placebo group,

particularly in the 300 mg QW (once a week) group, where there was a higher frequency of TEAEs, especially hypersensitivity events. Notably, treatment-related TEAEs and injection-site reactions were specific to the 300 mg QW group. In Rosenson et al. study [23] severe adverse events were recorded in seven patients in evinacumab arm, although claimed by the investigators to be unrelated to the medications, they were coronary or cerebral atherosclerotic events, indeed the actual hard cardiovascular endpoints to be evaluated [23]. It is crucial to note that these fatalities were not attributed to the trial drug but were linked to underlying heart disease, without giving a logical explanation as to why mortality was higher in evinacumab arm, compared to the placebo despite having the same refractory hypercholesterolemia, which is considered a study limitation. The management approach did not involve specific interventions related to Evinacumab but focused on addressing the broader health condition contributing to the adverse outcome.

Clinical implications and future directions

The combined findings from various clinical trials on evinacumab's efficacy present significant implications for clinical practice, future research, and potential updates to clinical guidelines. Evinacumab stands out as a valuable addition to therapeutic options for patients with FH. Its consistent efficacy in reducing LDL cholesterol levels, particularly in refractory cases, suggests its potential role in managing challenging lipid disorders. The robust impact on LDL-P and other lipid profiles positions evinacumab as a potential breakthrough for patients with limited treatment options. Despite the promising findings, there is a need for ongoing research, particularly in the form of long-term studies with larger and more diverse populations. The current evidence, while compelling, often stems from trials with limited sample sizes, specific patient populations, and varying methodologies. Future research should focus on establishing sustained efficacy and safety profiles across different demographic groups, ensuring a more comprehensive understanding of evinacumab's potential.

Pending further confirmation through rigorous research, evinacumab could influence guidelines for managing refractory hypercholesterolemia. Its unique mechanism of action demonstrated efficacy, and relatively favorable safety profile position it as a candidate for inclusion in clinical guidelines for treating severe lipid disorders. However, this recommendation should be substantiated by further robust evidence. The safety profile of evinacumab, as indicated by various trials, appears favorable. Treatment-emergent adverse events are relatively low, with the most common events being manageable and not leading to treatment discontinuation. This suggests that evinacumab is generally well-tolerated among diverse patient populations. Future research should investigate safety considerations, especially in prolonged and real-world use. Long-term safety data and post-marketing surveillance are essential to uncover any potential rare adverse events that may not be apparent in smaller clinical trials. Understanding the safety parameters in varied populations and different administration methods will contribute to a more comprehensive safety profile.

The instances of deaths reported in association with evinacumab underline the importance of a clinical approach. As evinacumab research advances, several key areas merit attention for future investigation and exploration. Future studies should prioritize inclusivity and diversity in patient populations to ensure the generalizability of findings across different demographic groups. This will contribute to a more comprehensive understanding of how evinacumab may benefit a broad range of individuals with severe hypercholesterolemia. Investigating real-world applications and outcomes of evinacumab beyond controlled clinical trial settings is essential. This includes exploring its effectiveness in routine clinical practice, potential challenges, and variations in response across different healthcare settings.

Limitations and strength of review

While our narrative synthesis provides valuable insights into the long-term efficacy, safety, and adverse events associated with evinacumab, it is important to note certain limitations. Primarily, the efficacy of evinacumab has been predominantly evaluated in terms of its impact on LDL lowering rather than directly assessing its effect on hard cardiovascular outcomes such as atherosclerotic cardiovascular complications. These complications include critical events such as the development of acute coronary syndrome, strokes, or peripheral atherosclerotic occlusive complications. Consequently, the absence of a direct evaluation of these outcomes within the current review limits full comprehension of the medication's overall cardiovascular efficacy and safety profile. In addition, the variability of study designs and methodologies across the included trials is a limitation. The heterogeneity in participant characteristics, treatment regimens, and outcome measures introduces challenges in directly comparing results and drawing universally applicable conclusions. Additionally, several studies had small sample sizes, potentially impacting the statistical power and generalizability of findings. Moreover, the available evidence predominantly stems from relatively short- to medium-term trials, and there needs to be more data on the long-term impact of evinacumab. Understanding sustained efficacy and safety profiles over extended periods is

crucial for informing clinical decision-making, especially in chronic conditions like familial hypercholesterolemia. Although this review acknowledges the efficacy of Evinacumab in the reduction of LDL cholesterol in familial hypercholesterolemia, the higher incidence of deaths in evinacumab arm in placebo-controlled RCT comparative studies mandates continued surveillance and holistic assessment of this medication before approving it.

Conclusion

The approval of evinacumab in the management of FH represents a pivotal advancement in addressing the challenges posed by this prevalent genetic disorder. This review explored the pharmacological underpinnings of evinacumab, shedding light on its mechanism of action as an IgG4 monoclonal antibody targeting angiopoietin-like 3 protein (ANGPTL3). The inhibition of ANGPTL3, a key regulator of lipid metabolism, demonstrates promise in addressing the distinctive lipid profiles observed in FH patients. Various clinical trials have underscored the current evidence on evinacumab's efficacy, showcasing its ability to significantly reduce LDL cholesterol levels, particularly in challenging cases of refractory hypercholesterolemia. These trials not only emphasise the short-term impact on lipid profiles but also hint at sustained efficacy over more extended periods, positioning evinacumab as a potential long-term solution for patients with limited treatment options. However, the efficacy findings, while promising, call for continued research efforts to establish the sustained impact of evinacumab and its safety profile. The varied responses observed in different patient populations and the instances of deaths reported underscore the importance of ongoing surveillance and clinical management. Furthermore, the current evidence presents a strong case for future research to address the limitations of existing studies, including small sample sizes and specific patient populations, to ensure robust generalizability and applicability to diverse demographic groups, and to emphasize its safety in this vulnerable population of familial hypercholesterolemia.

The clinical implications of evinacumab are significant, heralding a new era in the therapeutic landscape for FH. Its unique mechanism of action, and consistent efficacy position it as a possible option in management protocols for familial hypercholesterolemia after further long-term studies to ensure safety. However, cautious optimism is warranted, pending further substantiation through rigorous research. Future research directions should focus on inclusivity, diversity, and real-world applications of evinacumab. Long-term studies with larger and more diverse populations are crucial for establishing sustained efficacy and safety profiles. The integration of evinacumab into clinical guidelines should be informed by evidence-based recommendations, emphasizing the importance of ongoing collaboration between researchers, clinicians, and guideline developers.

Abbreviations

FH	Familial hypercholesterolemia
LDL-C	Low-density lipoprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
HDL	High-density lipoprotein
TG	Triglycerides
CAD	Coronary artery disease
ANGPTL3	Angiopoietin-like 3 protein
LPL	Lipoprotein lipase
EL	Endothelial lipase
VLDL	Very low-density lipoprotein
LDL-P	Low-density lipoprotein particle
ApoB	Apolipoprotein B
Lp(a)	Lipoprotein(a)
CCTA	Coronary computed tomography angiography
IgG4	Immunoglobulin G4
VEGF	Vascular endothelial growth factor
SC	Subcutaneous
IV	Intravenous
TEAEs	Treatment-Emergent Adverse Events
PCSK9	Proprotein convertase subtilisin/kexin type 9 (PCSK9)

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Authors' contributions
GO conceptualized the study. All authors were involved in the literature review. NA and EK extracted the data from the reviewed studies. All authors wrote the final and first drafts. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Not applicable.

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Not applicable.

Competing interests
The authors declare that they have no competing interests.

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