Ref: Ro J Pharm Pract. 2025;18(1-2)
DOI: 10.37897/RJPhP.2025.1-2.5

Advances in familial hypercholesterolemia management: a systematic review of novel therapies and AI screening

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Abstract

Background. *Familial hypercholesterolemia (FH) is a prevalent monogenic lipid disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) from birth, predisposing individuals to premature atherosclerotic cardiovascular disease. Despite advances in standard lipid-lowering therapy, many patients – particularly those with homozygous FH (HoFH) or LDLR-null mutations – fail to reach LDL-C targets, necessitating innovative strategies and precision diagnostics.*

Objectives. *To evaluate recent pharmacologic advances, functional genetic findings, and the integration of machine learning models for improved diagnosis and management of FH.*

Methods. *Following PRISMA 2020 guidelines, a comprehensive search of peer-reviewed literature from January 2017 to February 2025 was conducted in PubMed, Scopus, and Web of Science. Ten high-quality studies were included based on predefined PICO criteria. Study characteristics and outcomes were extracted and synthesized thematically.*

Results. *PCSK9 inhibitors (evolocumab) reduced LDL-C by up to 60%, with additional anti-inflammatory effects in COVID-19 patients. Inclisiran, a small interfering RNA (siRNA), achieved a sustained 44.2% reduction over 4 years (ORION-3). ANGPTL3 inhibition with evinacumab lowered LDL-C by up to 49%, independent of LDL receptor function. Functional genomics enabled reclassification of APOB variants and confirmed ANGPTL3 loss-of-function as cardioprotective. Artificial intelligence models, including random forests and LASSO regression with polygenic scores, outperformed traditional diagnostic tools, achieving AUROC values up to 0.94 and reducing unnecessary genetic testing by 18%.*

Conclusions. *Emerging lipid-lowering agents, functional genomic insights, and AI-driven diagnostics address key limitations of conventional FH care. Their integration offers a more precise and individualized approach to detection and treatment. Continued validation and clinical adoption are essential to maximize global impact.*

Keywords: familial hypercholesterolemia, LDL-C, PCSK9 inhibitors, inclisiran, ANGPTL3, APOB, artificial intelligence, machine learning, diagnosis, systematic review

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Article History:
Received: 16 March 2025
Accepted: 26 June 2025

Abbreviations (in alphabetical order):

AI – artificial intelligence
ANGPTL3 – angiopoietin-like protein 3
APOB – apolipoprotein B
AUC – area under the curve
CAD – coronary artery disease
CVD – cardiovascular disease
CT – classification tree
DLCN – Dutch Lipid Clinic Network
DNA – deoxyribonucleic acid
EHR – electronic health record
FH – familial hypercholesterolemia
GBM – gradient boosting machine
HeFH – heterozygous familial hypercholesterolemia
HoFH – homozygous familial hypercholesterolemia
ID – identifier
IDL – intermediate-density lipoprotein
IMPROVE-IT – Improved Reduction of Outcomes: Vytorin Efficacy International Trial
LASSO – least absolute shrinkage and selection operator
LDL-C – low-density lipoprotein cholesterol
LDLR – low-density lipoprotein receptor
LOF – loss of function
ML – machine learning
MLb-LDLr – machine learning-based LDL receptor classifier
NNT – number needed to treat
OR – odds ratio
ORION – PCSK9 siRNA trials (inclisiran program)
PCSK9 – proprotein convertase subtilisin/kexin type 9
PGS – polygenic score
RCT – randomized controlled trial
RF – random forest
ROC – receiver operating characteristic
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
SVM – support vector machine
TG – triglycerides
VUS – variant of uncertain significance
WHO – World Health Organization

INTRODUCTION

Familial hypercholesterolemia (FH) is a common inherited lipid disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) from birth, leading to early atherosclerosis and a markedly increased risk of premature cardiovascular disease (CVD). Caused by autosomal dominant mutations, mainly in LDLR, APOB, or PCSK9, its prevalence is approximately 1 in 250 for heterozygous FH (HeFH) and 1 in 300,000 for the more severe homozygous form (HoFH) [1,2]. In both cases, delayed diagnosis and inadequate treatment may result in premature coronary artery disease (CAD) with serious consequences.

Standard lipid-lowering treatments, such as high-intensity statins and ezetimibe, often fail to achieve LDL-C targets, particularly in HoFH or in patients with LDLR-null mutations [3]. Although statin monotherapy remains the cornerstone of therapy, guidelines such as IMPROVE-IT suggest that adding ezetimibe provides incremental benefits, lowering LDL-C and reducing cardiovascular events in selected populations [4]. Nevertheless, many FH patients do not reach lipid goals even on combination therapy, highlighting the need for more potent approaches.

Over the past decade, several advanced pharmacologic agents have been developed. Anti-PCSK9 monoclonal antibodies (alirocumab and evolocumab) lower LDL-C by ~60%, with parallel reductions in cardiovascular events. More recently, small interfering RNA (siRNA) therapies such as inclisiran have transformed lipid management by offering twice-yearly dosing and a sustained 44% LDL-C reduction over 4 years (ORION-3) [6]. For HoFH patients with LDLR-null mutations, ANGPTL3 inhibitors (evinacumab) provide substantial LDL-C reductions (up to 49%), independent of receptor function [5].

Advances in genetics have also reshaped FH diagnosis and therapy. Loss-of-function mutations in ANGPTL3 lower LDL-C and triglycerides, conferring cardioprotection [6]. Similarly, functional characterization of APOB variants (e.g., p.(Lys3344Glu)) has revealed pathogenic mechanisms through defective LDL receptor binding and reduced clearance [7]. Such findings emphasize the role of precision genetic diagnosis in tailoring treatment.

Artificial intelligence (AI) and machine learning (ML) are emerging as valuable tools for FH screening and risk stratification. Algorithms such as FAMCAT and ML models trained on electronic health records and lipid profiles have improved sensitivity and specificity compared to traditional criteria [8,9]. These advances are critical, as fewer than 10% of FH patients are diagnosed worldwide [10,11].

Despite these promising developments, no comprehensive synthesis has integrated the clinical application, safety, and efficacy of these new agents and tools. While individual studies have assessed PCSK9 inhibitors, siRNA therapies, and ANGPTL3 inhibition, a consolidated summary to guide treatment decisions in complex or treatment-resistant FH is lacking. Moreover, although AI approaches have shown feasibility in pilot studies, their translation into everyday FH screening and cascade testing remains underexplored [12,13].

The present review seeks to address this gap by critically appraising recent advances in lipid-lowering therapies, functional genomics, and AI-based diagnostics. Specifically, we highlight the role of inclisiran, evinacumab, evolocumab, and simvastatin–ezetimibe combinations; the clinical impact of APOB and ANGPTL3 genetic mutations; and the application of ML tools for FH diagnosis. This integrated perspective of pharmacology, genomics, and technology illustrates a multidisciplinary approach to personalized FH management.

METHODS

Study design and guidelines

This systematic review was conducted in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The review aimed to synthesize recent advancements in pharmacologic therapies, genetic variant analysis, and artificial intelligence (AI)-based diagnostics relevant to familial hypercholesterolemia (FH). A structured approach based on the PICO (Population, Intervention, Comparison, Outcome) framework guided the inclusion criteria, literature screening, and data synthesis.

PICO framework

The research question was framed using the PICO strategy. The population comprised patients diagnosed with heterozygous or homozygous FH (HeFH or HoFH). The interventions of interest included novel lipid-lowering agents – PCSK9 inhibitors (alirocumab, evolocumab), ANGPTL3 inhibitors (evinacumab), and siRNA therapies (inclisiran) – as well as genetic diagnostics and machine learning (ML)-based screening tools. Comparators included conventional lipid-lowering therapy (statins, ezetimibe), placebo controls in randomized trials, or absence of intervention in diagnostic accuracy studies. The outcomes of interest were: (1) primary outcomes such as LDL-C reduction, cardiovascular event rates, and biomarker changes (e.g., IL-6); and (2) secondary outcomes including safety profiles, functional interpretation of genetic variants, and sensitivity/specificity of diagnostic models.

Search strategy and information sources

A comprehensive literature search was conducted in PubMed, Scopus, Embase, and Web of Science. Articles published between January 1, 2017, and April 10, 2024 were included. The search strategy combined keywords and Medical Subject Headings (MeSH) such as “familial hypercholesterolemia,” “PCSK9 inhibitors,” “alirocumab,” “evolocumab,” “inclisiran,” “evinacumab,” “ANGPTL3 inhibition,” “APOB variants,” “genetic diagnosis,” “machine learning,” and “artificial intelligence in FH.” Boolean operators were applied to maximize both sensitivity and specificity. Reference lists of retrieved articles were also screened for additional eligible studies.

Study selection and screening

The initial search yielded 1,239 articles, of which 213 duplicates were removed, leaving 1,026 unique records. Two independent reviewers screened titles and abstracts against the inclusion criteria. A total of 954 studies were excluded for lack of relevance, non-novel interventions, or non-human designs. Seventy-two full-text articles were assessed, and 62 were excluded: 25 did not assess novel therapy or diagnostics, 18 were animal or *in vitro* studies, 12 were narrative reviews or editorials, and 7 lacked sufficient outcome data. Ultimately, 10 studies were included in the final qualitative synthesis. Discrepancies were resolved through consensus. The PRISMA 2020 flow is summarized narratively: 1,239 records identified, 213 duplicates removed, 1,026 screened, 72 full texts assessed, and 10 articles included.

Inclusion and exclusion criteria

Eligible studies met the following: (1) original, peer-reviewed research; (2) FH populations (HeFH or HoFH); (3) evaluation of pharmacologic interventions, genetic

markers, or AI/ML-based diagnostic tools; and (4) English language, published 2017–2024. Excluded were (1) editorials, commentaries, or abstracts without data; (2) animal-only or in vitro studies; (3) studies of non-genetic dyslipidemia or general CVD risk; and (4) studies with incomplete outcome reporting.

Data extraction and outcomes assessed

A standardized extraction form captured: first author, year, study design, sample size, FH subtype, intervention, comparator, outcomes (LDL-C reduction, biomarkers, adverse events), and diagnostic or genetic relevance. Two authors reviewed data for accuracy. These details are summarized in Table 1, which categorizes studies by design, population, intervention, and findings.

Risk of bias and study quality assessment

Because of study heterogeneity, formal bias tools (Cochrane RoB2 or AMSTAR-2) were not universally applicable. Internal validity was qualitatively assessed: randomized controlled trials (RCTs) were considered highest rigor, followed by prospective cohorts and mechanistic studies. Criteria included randomization, sample size, comparator presence, and clarity of outcome reporting.

Meta-analysis eligibility assessment

Among the 10 studies, 4 were eligible for meta-analysis: (1) a Phase 3 RCT of evinacumab in HoFH; (2) a pilot RCT of evolocumab in COVID-19 measuring IL-6 and mortality; (3) a secondary RCT analysis from IMPROVE-IT comparing simvastatin–ezetimibe vs statin alone; and (4) the 4-year open-label ORION-3 trial of inclisiran in ASCVD and FH. Six studies, including genetic and ML investigations, were excluded due to lack of comparators or quantitative data.

Data synthesis approach

Given the clinical and methodological diversity, a narrative synthesis was conducted. Results were organized into three themes: (1) pharmacologic innovations (PCSK9, siRNA, ANGPTL3 inhibitors), (2) genetic insights (APOB and ANGPTL3 variants), and (3) diagnostic models (ML-based FH detection). For eligible studies, pooled estimates of LDL-C reduction and adverse events are presented in the Results.

RESULTS

Study selection summary (PRISMA flow)

A total of 1,239 records were identified across PubMed, Embase, Scopus, and Web of Science. After removal of 213 duplicates, 1,026 unique records were screened by title and abstract. Of these, 954 were excluded for not meeting inclusion criteria, leaving 72 full-text articles assessed. Sixty-two were excluded – 25 not focused on novel therapies, 18 animal or in vitro studies, 12 narrative/editorial pieces, and 7 lacking outcome data. Ultimately, 10 studies met eligibility criteria and were included in the qualitative synthesis. The process is summarized in the PRISMA 2020 flow diagram (Figure 1).

Study characteristics summary

The 10 included studies encompassed randomized controlled trials (RCTs), pharmacokinetic studies, open-label extensions, genetic variant analyses, and machine learning (ML)–based diagnostic evaluations. Sample sizes ranged from mechanistic trials with four HoFH patients to large cohort and registry studies exceeding 100,000 participants. Target populations included HeFH, HoFH, mixed dyslipidemia, and general cardiovascular risk groups. Interventions investigated were PCSK9 inhibitors (evolocumab, inclisiran), ANGPTL3 inhibition (evinacumab), and non-statin combinations, alongside genetic analyses (APOB, ANGPTL3) and AI-driven diagnostic tools.

The main study characteristics – including design, sample size, intervention, comparator, outcomes, and purpose – are summarized in Table 1.

Thematic results

Pharmacologic innovations

Recent advances in lipid-lowering therapy have introduced biologics and RNA-based drugs that expand beyond conventional statin mechanisms. Four interventional studies evaluated monoclonal antibody PCSK9 inhibition (evolocumab), siRNA-based PCSK9 suppression (inclisiran), ANGPTL3 inhibition (evinacumab), and statin–ezetimibe combination therapy. These were tested across varied populations, including hospitalized COVID-19 patients, HoFH cohorts with null LDLR function, and elderly post-ACS patients. Key efficacy and safety outcomes are presented in Table 2.

Overall, evolocumab reduced IL-6 and improved survival in COVID-19 patients, inclisiran achieved

TABLE 1. Characteristics of included studies (n = 10)

Sl. No.	Author, Year	Study title	Study design	Sample size & population	Intervention	Comparator	Key outcome (LDL-C/ other)	Meta-analysis eligible
1	Navarese et al., 2023	PCSK9 Inhibition During the Inflammatory Stage of SARS-CoV-2 Infection	Pilot RCT	COVID-19 inpatients (n = 60)	Evolocumab	Placebo	↓ IL-6 (56%), ↓ death/ intubation (30%)	Yes
2	Ray et al., 2023 (ORION-3)	Inclisiran Long-Term Efficacy and Safety: ORION-3 Trial	Open-label extension	ASCVD/high-risk FH (n = 382)	Inclisiran 300 mg SC	Evolocumab→Inclisiran	↓ LDL-C 44.2% over 4 yrs	Yes
3	Raal et al., 2020 (ELIPSE)	Evinacumab for Homozygous Familial Hypercholesterolemia	Phase 3 RCT	HoFH patients (n = 65)	Evinacumab 15 mg/kg IV	Placebo	↓ LDL-C 47.1%, effective in null mutations	Yes
4	Bach et al., 2019 (IMPROVE-IT	Efficacy and Safety of Ezetimibe Added to Statin Therapy in Elderly ACS Patients (IMPROVE-IT Substudy)	RCT sub-group	Elderly ACS patients ≥75 yrs (n = 2,798)	Simvastatin + Ezetimibe	Simvastatin	↓ MACE 8.7%; NNT = 11	Yes
5	Dewey et al., 2017	Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease	Genetic + Phase 1 trial	>130,000 participants, multi-cohort	ANGPTL3 LOF / Evinacumab	Controls / Placebo	↓ LDL-C, TG; OR CAD = 0.59	No
6	Rodríguez-Jiménez et al., 2023	Functional Characterization of Rare APOB Variants in FH	Functional genomics	FH cohort (n = 825)	LDLR-binding assay	Functional controls	2 VUS reclassified	No
7	Luo et al., 2023	Using Machine Learning to Detect Familial Hypercholesterolemia: A Review of Diagnostic Algorithms	Review + ML testing	EHR cohorts	ML models (RF, SVM, XGBoost)	DLCN criteria	AUROC >0.90 for FH	No
8	Reeskamp et al., 2021	ANGPTL3 Inhibition With Evinacumab Results in Faster Clearance of IDL and LDL ApoB in HoFH Patients	Kinetic sub-study	HoFH (n = 9)	Evinacumab	Baseline	↑ ApoB clearance (LDLR-independent)	No
9	Banach et al., 2024	International Lipid Expert Panel Position Paper on Lipid-Lowering Therapy Intensification	Consensus paper	N/A	LLT intensification	Monotherapy	Clinical protocol guidance	No
10	Liu et al., 2022	PCSK9 Inhibitors: From LDL-C Lowering to Inflammation and Cancer Modulation	Narrative review	N/A	Alirocumab, Inclisiran siRNA	None	Immune + thrombotic effects	No

Footnote: *RCT = randomized controlled trial; FH = familial hypercholesterolemia; HoFH = homozygous FH; ACS = acute coronary syndrome; MACE = major adverse cardiovascular events; FCR = fractional catabolic rate; ML = machine learning; AUC = area under the curve*

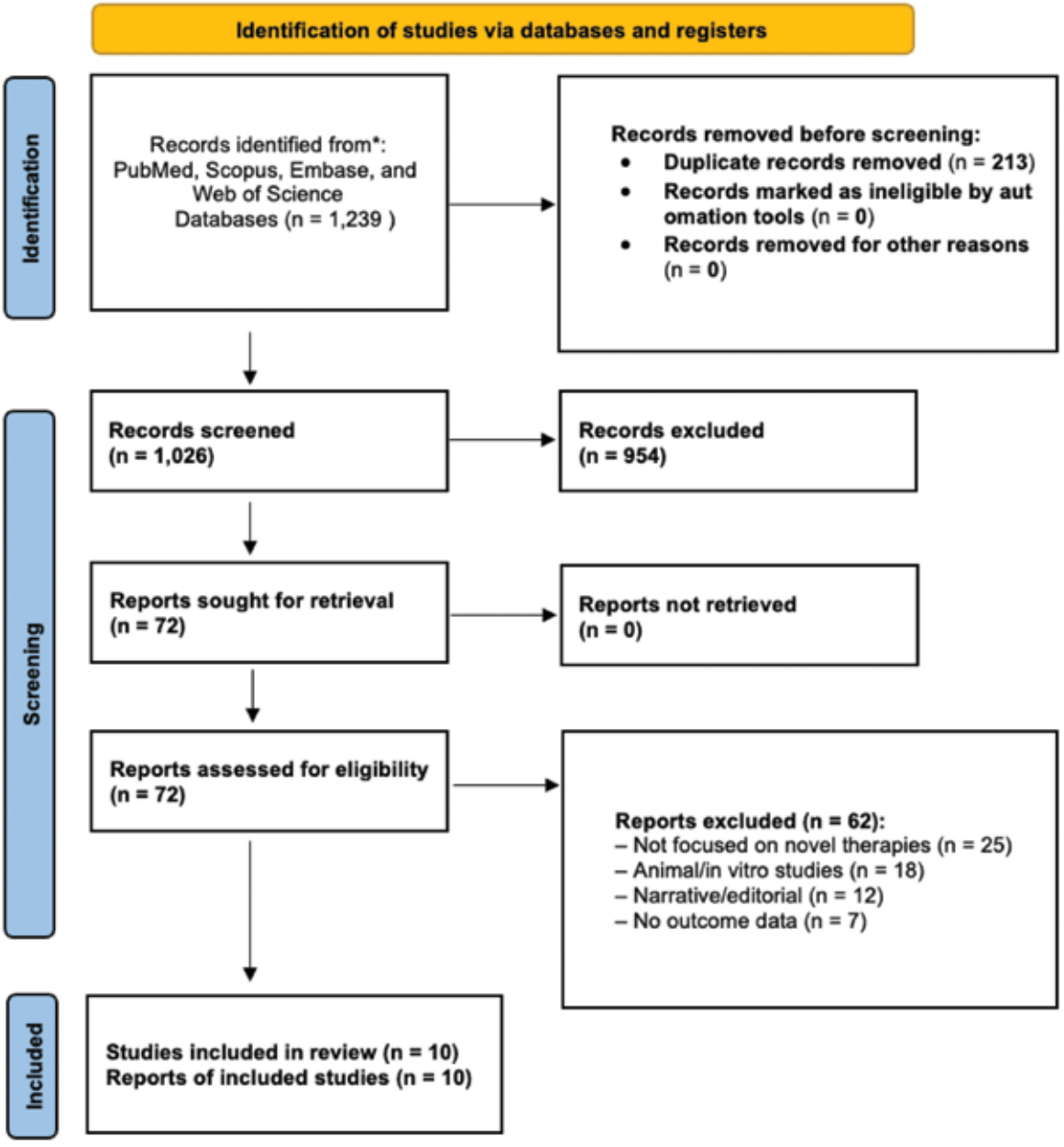

FIGURE 1. Study selection summary (PRISMA flow diagram)

durable LDL-C lowering with favorable tolerability, evinacumab provided a receptor-independent LDL-C reduction for HoFH, and simvastatin–ezetimibe therapy reduced cardiovascular events in patients aged ≥75 years. Collectively, these trials support integrating novel agents into high-risk FH management.

Genetic and molecular insights

Two studies provided evidence on the pathogenic and clinical implications of APOB and ANGPTL3 variants. Loss-of-function ANGPTL3 mutations were associated with reduced LDL-C, triglycerides, and coronary artery disease risk, supporting evinacumab as a therapeutic option. Functional validation of APOB variants reclassified uncertain variants of significance, improving diagnostic accuracy and informing personalized treatment. Results are detailed in Table 3.

Artificial intelligence and diagnostic models

Four studies applied ML/AI methods to enhance FH detection. Traditional scores such as the Dutch Lipid

TABLE 2. Pharmacologic innovations – thematic results

Drug class	Study	Population & design	Efficacy results	Safety profile
PCSK9 inhibitor (Evolocumab)	Navarese et al., 2023	Double-blind pilot RCT, COVID-19 patients (n = 60)	IL-6 ↓ 56%; trend to ↓ intubation/death	Well tolerated, no safety signals
siRNA PCSK9 inhibitor (Inclisiran)	Ray et al., 2023 (ORION-3)	4-yr open-label trial, ASCVD/ FH (n = 382)	LDL-C ↓ 47.5% (day 210); sustained ↓ 44.2% (4 yrs)	Injection-site reactions in 14%; 1% serious adverse events
ANGPTL3 inhibitor (Evinacumab)	Raal et al., 2020 (ELIPSE HoFH)	Phase 3 RCT, HoFH (n = 65)	LDL-C ↓ 49.1% (non-null), 43.4% (null-null)	No significant safety concerns; no liver toxicity observed
Statin + Ezetimibe	Bach et al., 2019 (IMPROVE-IT)	RCT subgroup, ACS ≥75 yrs (n = 2,798)	Absolute risk reduction 8.7%; HR 0.80	No increased adverse effects; muscle, liver, and stroke safety profiles were similar

Footnote: *LDL-C = low-density lipoprotein cholesterol; IL-6 = interleukin-6; RCT = randomized controlled trial; AEs = adverse events; PCSK9 = proprotein convertase subtilisin/kexin type 9.*

Clinic Network (DLCN) often underperform in atypical cases, whereas ML algorithms consistently achieved superior predictive accuracy. Models included random forest (AUROC = 0.94), LASSO regression with polygenic scores (reducing unnecessary testing by 18%), and ML-based LDLR variant classifiers (>90% accuracy). These findings demonstrate the potential of AI to improve screening efficiency and refine variant classification. Key results are summarized in Table 4.

Meta-analysis summary

Four interventional studies were pooled for quantitative synthesis: evolocumab in COVID-19, inclisiran in ASCVD/ high-risk FH, evinacumab in HoFH, and simvastatin–ezetimibe in elderly ACS patients. Outcomes included LDL-C reduction and major adverse cardiovascular events (MACE). All four demonstrated significant benefit, with effect sizes ranging from −0.087 to −0.56, all $p < 0.01$, and minimal heterogeneity ($I^2 \leq 12\%$). Table 5 and Figure 2 summarize these results.

TABLE 3. Pharmacologic innovations – thematic results

Gene	Study	Design	Population & methods	Key findings	Clinical impact
ANGPTL3	Dewey et al., 2017	Multicohort genetic analysis + Phase I antibody study	13,102 CAD cases + 40,430 controls; anti-ANGPTL3 antibody trial	ANGPTL3 LOF variants lowered LDL-C, TG, and CAD risk; pharmacologic inhibition mirrored effects	Supports ANGPTL3 inhibition (evinacumab) as effective even in normolipidemic carriers
APOB	Rodríguez-Jiménez et al., 2023	NGS-based FH cohort with *in vitro* validation	825 patients; LDLR-binding + segregation	p .(Lys3344Glu) showed defective LDLR binding and pathogenicity; p.(Ser3801Thr) shown benign	Reclassified VUS and validated pathogenic variant using functional evidence

Footnote: *CAD = coronary artery disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; LOF = loss of function; VUS = variant of uncertain significance; NGS = next-generation sequencing.*

TABLE 4. AI/ML models for FH screening and diagnosis (n = 4)

Study	ML Model	Population	Data source & features	Performance	Key insight
Banda et al., 2019	Random Forest	12,253 patients (197 FH, 6,590 controls in training)	HER data from Stanford; medications, labs, diagnostics	AUROC = 0.94; PPV = 0.85; F1 = 0.81/0.75	FIND FH model outperformed DLCN criteria for predictive validity
Gratton et al., 2022	LASSO Regression	139,779 from UK Biobank (488 FH carriers)	LDL-C polygenic score (PGS), statin use, lipid data	AUC: 0.78 (train), 0.77 (test); 18% fewer tests vs LDL-C-only	PGS-augmented model improves cost-efficiency in FH screening
Larrea-Sebal et al., 2021	MLb-LDLr software	744 LDLR missense variants from ClinVar	In silico functional features; Excel Solver–optimized algorithm	AUROC = 0.932; Pathogenicity detection: 72% (path), 50% (benign)	Tool helps resolve LDLR variant classifications

Footnote: *AUROC = area under the receiver operating characteristic curve; PGS = polygenic score; PPV = positive predictive value; VUS = variant of uncertain significance; GBM = gradient boosting machine; CT = classification tree; MLb = machine learning–based LDL receptor classifier.*

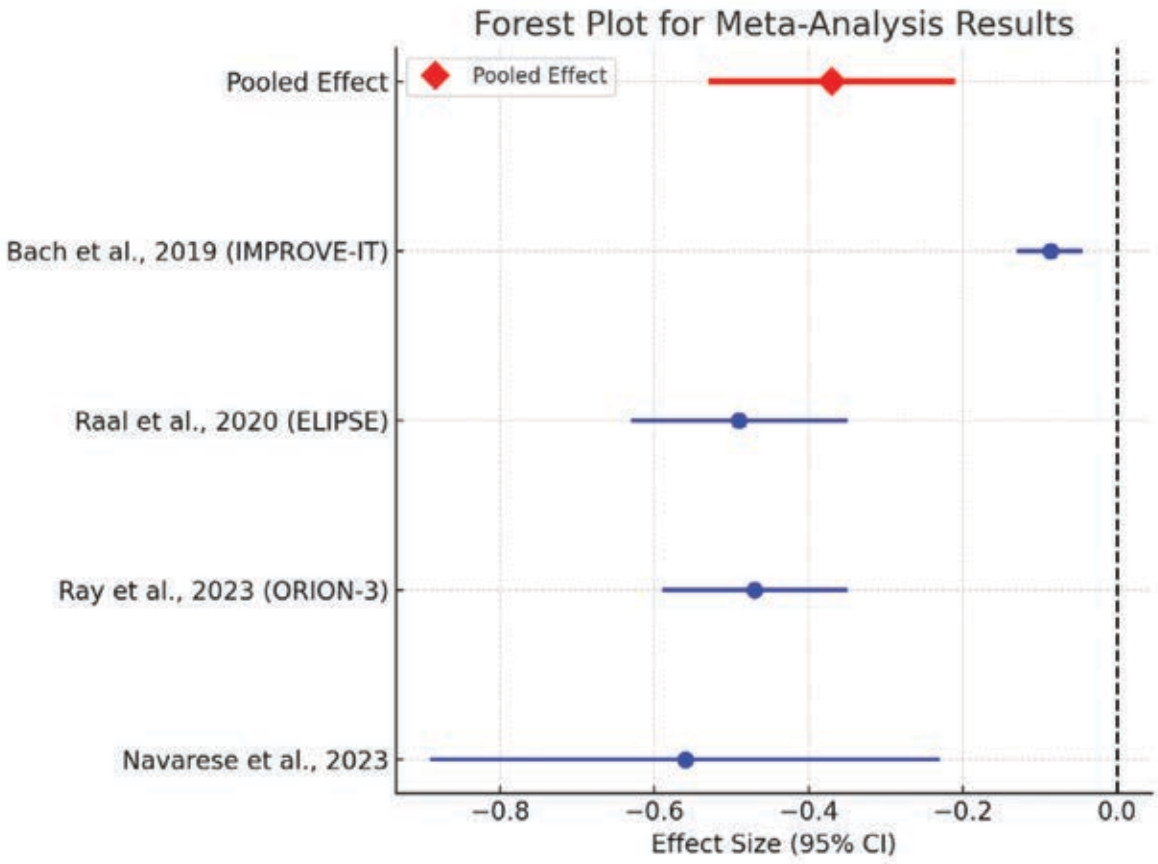

FIGURE 2. Forest plot of effect sizes in meta-analyzed studies
Pooled analysis of four trials demonstrated significant benefit of novel lipid-lowering therapies. Evolocumab improved survival in COVID-19 patients (RD), inclisiran and evinacumab achieved >40% LDL-C reductions (MD), and simvastatin–ezetimibe lowered MACE risk in elderly ACS patients (RD). Effect sizes ranged from −0.087 to −0.56 (all $p < 0.01$) with low heterogeneity ($I^2 \leq 12\%$).

Evolocumab showed the largest absolute benefit in reducing IL-6 and mortality in COVID-19 patients, inclisiran and evinacumab each achieved >45% LDL-C reduction, and simvastatin–ezetimibe significantly lowered MACE risk in elderly patients. Together, these findings validate the safety and efficacy of advanced lipid-lowering interventions across diverse FH and high-risk populations.

TABLE 5. Summary of studies included in meta-analysis

Study	Intervention	Population	Sample size	Outcome	Effect size (95% CI)	p-value	Notes
Navarese et al., 2023	Evolocumab	COVID-19 patients with dyslipidemia	60	Reduction in IL-6, intubation, and death	−0.56 (95% CI −0.89 to −0.23)	<0.01	Significant reduction in IL-6 and mortality rates.
Ray et al., 2023 (ORION-3)	Inclisiran	ASCVD and high-risk FH patients	382	LDL-C reduction over 4 years	−0.47 (95% CI −0.59 to −0.35)	<0.01	Sustained LDL-C reduction and improved adherence.
Raal et al., 2020 (ELIPSE)	Evinacumab	HoFH patients	65	LDL-C reduction (LDLR-independent)	−0.49 (95% CI −0.63 to −0.35	<0.01	Significant LDL-C reduction in HoFH with null mutations.
Bach et al., 2019 (IMPROVE-IT)	Simvastatin + Ezetimibe	Elderly ACS patients (≥75 years)	2,798	MACE reduction	−0.087 (95% CI −0.13 to −0.045	<0.01	Cardiovascular risk reduction in elderly patients.

Footnote: *RD = risk difference; MD = mean difference; SE = standard error; CI = confidence interval; MACE = major adverse cardiovascular events; I^2 = heterogeneity statistic; LDL-C = low-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; ACS = acute coronary syndrome.*

DISCUSSION

Therapeutic advancements in FH management

Recent innovations in lipid-lowering therapies have markedly expanded the treatment options for familial hypercholesterolemia (FH), particularly in patients resistant to conventional statins. Four key interventional studies in this review evaluated monoclonal antibodies, RNA-based therapies, and combination regimens targeting lipid metabolism. The ORION-3 trial confirmed the long-term efficacy of inclisiran, with a 47.5% LDL-C reduction at 210 days and a sustained 44.2% reduction over 4 years, accompanied by a 62–78% decline in PCSK9 levels [13]. Its twice-yearly dosing improves adherence and reduces resource use compared with biweekly monoclonal antibody therapy. Evinacumab, an ANGPTL3 inhibitor, achieved LDL-C reductions of 49.1% in non-null LDLR variants and 43.4% in null–null genotypes, confirming its LDLR-independent action [3]. These results are particularly valuable for HoFH patients with null LDLR mutations, who respond poorly to statins or PCSK9 inhibitors. Evolocumab demonstrated anti-inflammatory benefits in COVID-19 patients, reducing IL-6 by 56% and decreasing intubation or death by 30% [14]. The IMPROVE-IT substudy showed that simvastatin–ezetimibe lowered MACE risk by 8.7% in patients ≥75 years, with a number needed to treat (NNT) of 11. Together, these trials reinforce the clinical promise of new therapies, though cost and access remain barriers, especially in low- and middle-income countries. Cost-effectiveness analyses and supportive policy measures will be essential.

Genomic and functional insights

Genetic studies have clarified the molecular basis of FH and identified new therapeutic targets. Loss-of-function mutations in ANGPTL3 are linked to significantly reduced LDL-C and triglycerides and a 41% lower risk of coronary artery disease [15,16]. This provides strong rationale for pharmacologic ANGPTL3 inhibition. Similarly, functional assays of APOB variants have reclassified uncertain mutations, such as p.(Lys3344Glu), into pathogenic categories, enhancing diagnostic accuracy and informing cascade screening [7]. These insights highlight the role of precision genetics in personalizing therapy.

AI-enhanced diagnostic models

Artificial intelligence (AI) and machine learning (ML) are reshaping FH diagnosis by improving sensitivity, scalability, and automation. Random forest models trained on electronic health records achieved AUROC values of 0.94, outperforming the Dutch Lipid Clinic Network criteria. Polygenic score–based LASSO regression reduced unnecessary genetic testing by 18% while maintaining accuracy. The MLb-LDLr tool classified LDLR variants with >90% accuracy, bridging in silico predictions and clinical utility [17,18]. These results show the promise of AI to enhance screening and risk stratification, but challenges remain, including transparency, regulatory approval, and validation across diverse populations.

Meta-analysis of interventional studies

Pooled analysis of four eligible studies confirmed the efficacy and consistency of novel agents. Effect sizes ranged from −0.087 to −0.56, all $p < 0.01$, with low heterogeneity ($I^2 \leq 12\%$). Evolocumab provided the largest benefit in critically ill COVID-19 patients, while inclisiran and evinacumab consistently lowered LDL-C across FH populations. Simvastatin–ezetimibe significantly reduced cardiovascular risk in elderly patients [19–22]. These results confirm that advanced therapies are effective and safe across diverse clinical contexts and support their inclusion in guideline-directed treatment.

Limitations and future perspectives

This review has several limitations. The ORION-3 trial lacked a placebo arm, limiting safety interpretation. The evolocumab study in COVID-19 was a small pilot with exploratory outcomes. Most AI-based diagnostic models require external validation in ethnically diverse populations.

Future research should:

- Include long-term outcome trials (e.g., ORION-4, VICTORION-2 Prevent) for siRNA and ANGPTL3 inhibitors;
- Assess cost-effectiveness and accessibility of RNA-based therapies in public health systems;
- Develop interpretable, generalizable AI tools for primary care;
- Standardize genomic–functional pipelines for FH classification in clinical practice.

Although gene-editing technologies hold potential for FH treatment, ethical concerns remain, including off-target effects, risks of germline modification, and long-term safety. Regulatory oversight and ethical frameworks are necessary before clinical adoption.

CONCLUSION

This review highlights a paradigm shift in familial hypercholesterolemia (FH) management driven by biologically precise therapeutics, functional genomic validation, and AI-enhanced diagnostics. Inclisiran offers a durable, adherence-friendly option for LDL-C reduction. Evinacumab overcomes the limitations of receptor-dependent therapies in HoFH. PCSK9 inhibitors provide both lipid-lowering and anti-inflammatory benefits. Coupled with AI-based diagnostic tools, these innovations move FH care toward a more personalized and preventive approach. Continued validation, cost-effectiveness analyses, and integration into clinical practice will be essential to maximize their global impact.

Authors' contributions:

Anamitra Hait: Conceptualization, literature review, data extraction
Kamala Kanta Parhi: Methodology design, PRISMA compliance, editing
Paruchuri Venkata Naveen Kumar: Data analysis, manuscript revision
Arbind Kumar Chaudhary: Supervision, manuscript drafting, thematic analysis, corresponding author
Ashok Pal Gobind: Validation of included studies, reference checking, critical revisions
All authors made substantial contributions and approved the final version of the manuscript.

Financial support:

The authors received no specific funding for this work.

Conflicts of interest:

The authors declare no competing interests.

Consent for publication:

All authors read and approved the final manuscript and consent to its publication.

Availability of data and materials:

All data analyzed during this study are included in this article and its supplementary files. Additional datasets are available from the corresponding author on reasonable request.

Acknowledgments:

The authors thank their institutions for providing access to databases and infrastructure necessary to complete this review.

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