# PCSK9 and ANGPTL3 inhibitors in homozygous familial hypercholesterolemia: A meta-analysis of randomized clinical trials

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**Abstract**

Background: The aim of this meta-analysis was to compare the efficacy of PCSK9 and ANGPTL3 inhibitors in patients with Homozygous familial hypercholesterolemia (HoFH) Methods: We systematically searched selected electronic databases until 30th November 2024. Main endpoint was the effect of lipid lowering therapy on lipid profile: total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and lipoproteins levels. The secondary endpoint was adverse clinical effects. Results: 12 trials involving a total of 392 patients with HoFH, were included in the meta-analysis. At a median follow-up of 12 months, the ANGPTL3i group demonstrated a greater reduction in mean TC [–4.27 mmol/L (165.1 mg/dL) vs. –1.37 mmol/L (52.9 mg/dL); p for subgroup <0.001], LDL-C [–3.51 mmol/L (135.7 mg/dL) vs. –1.81 mmol/L (69.9 mg/dL); p for subgroup <0.001], and TG [–0.61 mmol/L (54.1 mg/dL) vs. –0.21 mmol/L (18.6 mg/dL); p for subgroup <0.001], but a smaller impact on HDL-C compared to those treated with PCSK9i. Lipids were reduced more in adults compared to children in the PCSK9i group (p<0.01) but not in the ANGPTL3i group (p=0.23). Likewise, Apo-B reduced more with ANGPTL3i compared to PCSK9i but Apo-A and Lipoprotein (a) remained comparable between the two groups. The treatment-related adverse events and discontinuation rates were not different between groups. Conclusions: PCSK9 inhibitors have lower efficacy in reducing lipid levels in HoFH patients compared to ANGPTL3 inhibitors, particularly in children. Their effectiveness in different functional variations of LDL-C receptors in HoFH patients needs to be established.

## INTRODUCTION

Homozygous familial hypercholesterolemia (HoFH) is an autosomal semidominant disease characterized by markedly high levels of low-density lipoprotein cholesterol (LDL-C) leading to an increased risk for premature atherosclerotic cardiovascular disease (ASCVD), high burden of CV outcomes and early mortality [1, 2]. It is caused by pathogenic variants in the LDL receptor (LDLR) gene or other genes affecting LDLR function [3]. HoFH affects approximately 1 in 160,000 to 360,000 individuals worldwide [4,5]. Despite its significant health implications, underdiagnosis and undertreatment remain major challenges in managing this condition. Current estimates suggest that approximately 30,000 people globally have HoFH; however, less than 5% of these are properly identified and treated [4, 5]. Genetic alterations in HoFH that result in minimal or absent LDL receptor (LDLR) expression (null homozygotes) lead to significantly higher LDL-C levels compared to alterations that only partially reduce LDLR expression, such as having two non-null alleles or one null and one non-null allele (non-null homozygotes) [6]. This distinction is crucial, as HoFH accelerates the onset of ASCVD, with individuals carrying null-null LDLR variants at a higher risk of premature ASCVD. Untreated patients with HoFH typically do not survive beyond the third decade, underscoring the importance of early intervention to optimally manage LDL-C and to lower the risk of CV events [7, 8].

Combination of lipid-lowering therapy (LLT), including different available therapies and lipoprotein apheresis (LA), is the cornerstone management of HoFH, alongside lifestyle modifications [1]. Guidelines recommend early initiation of multiple LLTs such as high-intensity statins, ezetimibe, PCSK9 inhibitors (evolocumab or alirocumab), angiopoietin-like 3 (ANGPTL3) inhibitors such as evinacumab and mipomersen, and lomitapide [1, 7, 9, 10, 11]. Statins and PCSK9 inhibitors, which upregulate hepatic LDL receptors, reduce LDL-C by LDLR alleles [1, 12, 13]. Lomitapide, acting independently of LDLR, is an alternative but carries some safety concerns including gastrointestinal issues and hepatic steatosis [14, 15]. Angiopoietin-like 3 (ANGPTL3) is a key regulator of lipid metabolism, primarily inhibiting lipoprotein lipase (LPL) and endothelial lipase. Evinacumab, an ANGPTL3 monoclonal antibody, has proved effective in patients aged [?]12 years, in reducing LDL-C by ˜50% in the ELIPSE HoFH trial when used alongside maximally tolerated LLTs and/or lipoprotein apheresis [16, 17]. The purpose of this meta-analysis was to evaluate and compare the efficacy and safety of PCSK9 and ANGPTL3 inhibitors in the treatment of HoFH.

## METHODS

*Search strategy and selection criteria*

We conducted the study in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. As this is a meta-analysis, there was no need for Institutional Review Board (IRB) approval or patient informed consent. To define the clinical question and formulate a comprehensive search strategy, we applied the PECOS model, focusing on population, intervention, comparison, outcomes, and study design (*Table S1* ).

Databases were systematically searched up to November 30, 2024. These included PubMed-Medline, EMBASE, Scopus, Google Scholar, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, using specific keywords to identify relevant studies: "Proprotein convertase subtilisin/kexin type 9" OR "PCSK9 inhibitors" OR "PCSK9i" OR Angiopoietin-like protein 3 inhibitors" OR "ANGPTL3 inhibitors" OR "ANGPTL3 i" OR "Alirocumab" OR "Evolocumab" OR "Evinacumab" AND "Homozygous Familial Hypercholesterolemia" OR "Homozygous FH" OR "HoFH" (*Table S2* ).To identify additional relevant studies, references from review articles and abstracts from key congresses, such as the European Society of Cardiology (ESC), European Atherosclerosis Society (EAS), American Heart Association (AHA), and American College of Cardiology (ACC) were reviewed. The wildcard term "*" was employed to enhance search sensitivity, with the search restricted to human studies published in English and no filters applied. Each article was independently evaluated by two reviewers (M.S. and D.G.). In cases of uncertainty regarding the suitability of a paper, the senior investigators (I.B. and M.B.) were consulted. The selected articles were assessed in full text, and data extraction was performed by the same researchers, while data analysis was conducted by two other researchers (S.B. and I.B.). Typically, the extracted data were compared with the original articles, and errors were corrected as needed. For each trial, the risk of bias was independently assessed by the same investigators using the revised Cochrane risk-of-bias tool for randomized trials (Cochrane RoB2 tool), which evaluates five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and the selection of reported results. The risk of bias in each study was categorized as "low," "high," or "unclear." [19].

Articles were considered eligible if they reported the treatment of HoFH patients with PCSK9 inhibitors (PCSK9i) or ANGPTL3 inhibitors (ANGPTL3i) under the following criteria: i) trials investigating the efficacy and/or safety of PCSK9i/ANGPTL3i pre-post-treatment in HoFH patients after treatment with standard lipid-lowering therapy (LLT); ii) studies using genetic and/or clinical criteria for the diagnosis of HoFH according to the available guidelines; and iii) trials with a follow-up period of at least 3 months. Exclusion criteria were: i) insufficient statistical data to test the efficacy and safety of treatment, ii) patients with heterozygous FH, iii) studies not in humans, and iv) ongoing studies (unless they had reported relevant interim results).

*Outcome variables*

The primary endpoint was to assess the efficacy and safety of PCSK9 inhibitors and ANGPTL3 in-

hibitors in patients with HoFH. Efficacy parameters for PCSK9i (Alirocumab, Evolocumab) and ANGPTL3i (Evonacumab) included changes in lipid profiles, such as total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and lipoprotein levels, including lipoprotein(a) (Lp(a)), apolipoprotein A (Apo-A) and apolipoprotein B (Apo-B). The secondary endpoint focused on safety, with parameters including the prevalence of adverse events (AEs), and inverse variance used for subgroup analyses between groups.

*Data synthesis and statistical analyses*

The meta-analysis was conducted using R Statistical Software (v3.5.1, Boston, MA, USA) with the 'meta' and 'metafor' packages for analysis, and RevMan (Review Manager Version 5.1, The Cochrane Collaboration, Copenhagen, Denmark). A two-tailed p-value of $< 0.05$ was considered statistically significant. Summary statistics are presented as weighted mean differences (WMD) with 95% confidence intervals (CIs). Mean and standard deviation (SD) values were estimated based on the method described by Hozo et al. [20]. A random-effects model (Der Simonian and Laird method) was used to estimate the pooled prevalence of adverse events across studies. The 95% CIs for the prevalence of adverse events were calculated using the binomial exact method (Clopper-Pearson) based on the proportion of cases and sample size. Inverse variance weighting was applied to each study in the meta-analysis. Results are illustrated in forest plots, the standard way of presenting individual study and meta-analysis outcomes. Sub-analyses were conducted to evaluate the effect of different types of lipid-lowering therapy (LLT) on lipid profiles and safety parameters. Meta-analyses were performed using the random-effects model. Heterogeneity across studies was assessed using the Cochrane Q test and the $I^2$ index, with $I^2 < 25\%$ indicating low, 25-50% moderate, and >50% high heterogeneity. The reduced maximum likelihood method ($tau^2$) was used to incorporate residual heterogeneity in the analysis [21]. Publication bias was assessed through visual inspection of funnel plots and Egger's test.

## RESULTS

Characteristics of included trials

An initial search yielded 4687 articles, which were screened for relevance, leading to the selection of 348 articles. Following a rigorous selection process, 12 trials involving 392 HoFH patients were included in the meta-analysis [22 – 33] (*Figure S1* ). Six RCTs used PCSK9i (n=152 patients) and in the other 6 RCTs the treatment with ANGTPL3i was applied (n=240 patients). The characteristics of included trials are presented in *Table 1* . The mean age of the patients was 31.7 ± 13 and 48.4% were females. 55.2% of patients were with CVD disease when included in the trials. The prevalence of White patients was significantly higher compared to the Black, Asian or other races (75.4, 2.4, 8.49, 11%, p<0.01; respectively).

When comparing the summary mean differences (SMD) of patients treated with LLTs, patients age in the groups of PCSK9i and ANGPTL,3i trials were similar (30.8±14.8 vs. 33.3±12.2, p=0.07). However, the prevalence of female patients and the presence of CVD were significantly lower in patients treated with PCSK9i compared to those treated with ANGPTL3i (p<0.01 for both), (*Table S3* ).

The mean baseline levels of TC [8.45 ± 3.2 mmol/L (326.7 ± 123.7 mg/dL) vs. 10.9 ± 3.9 mmol/L (421.5 ± 150.8 mg/dL); $p < 0.001$], LDL-C [7.17 ± 3.3 mmol/L (277.3 ± 127.6 mg/dL) vs. 9.64 ± 3.7 mmol/L (372.8 ± 143 mg/dL); $p < 0.001$], and Lp(a) [34.9 ± 12.9 mg/dL vs. 60.1 ± 36 mg/dL; $p < 0.001$] were significantly lower in the ANGPTL3i group compared to the PCSK9i group, whereas HDL-C, TG, Apo-B, and Apo-A levels did not differ significantly between the groups ($p > 0.05$ for all; *Figure S2* ).

*Comparative efficacy of PCSK9i and ANGPTL3i on lipid profiles and lipoproteins*

At a median follow-up of 12 months, using an inverse analysis model, the ANGPTL3i group had greater reduction of mean TC [–4.27 mmol/L (165.1 mg/dL) vs. –1.37 mmol/L (52.9 mg/dL); $p_{\text{for subgroup}}$mmol/L (69.9 mg/dL); $p_{\text{for subgroup}}$ <0.001], and TG levels [–0.61 mmol/L (54.1 mg/dL) vs. –0.21 mmol/L (18.6 mg/dL); $p_{\text{for subgroup}}$ <0.001] compared to the PCSK9i group. In contrast, HDL-C increased slightly, more with PCSK9i than with ANGPTL3i [0.08 mmol/L (3.09 mg/dL) vs. –0.21 mmol/L (-8.12 mg/dL); $p_{\text{for subgroup}} = 0.001$] (*Figure S3 & S4, Graphical Abstract* ). Likewise, Apo-B decreased more with ANGPTL3i compared

to PCSK9i [–0.81 g/L vs. –0.21 g/L; p < 0.001], but Lp(a) reduction was comparable between the two groups (–9.3 vs. –12.9 mg/dl; p = 0.53), and Apo-A remained unaffected in both groups (p = 0.13; *Figure S5* ). A summary of the efficacy of ANGPTL3 inhibitors and PCSK9 inhibitors is presented in**Figure 1** . In the age-based subgroup analysis, PCSK9i resulted in a significantly greater reduction of mean LDL-C in adults compared to children [–1.87 mmol/L (–72.3 mg/dL) vs. –0.59 mmol/L (–22.8 mg/dL); p < 0.001]. In contrast, no significant age-related difference was observed with ANGPTL3i [–3.53 mmol/L (–136.5 mg/dL) vs. –3.40 mmol/L (–131.5 mg/dL); p = 0.22; *Figure S6* ].

*Safety and tolerability of PCSK9i and ANGPTL3i in HoFH patients*

At the end of the follow-up period, no significant difference was observed between the groups with regards to the prevalence of TEAE or treatment discontinuation (p > 0.05 for both). The prevalence of gastroenteritis, abdominal pain, nausea, and vomiting was higher, while injection site reactions, upper respiratory tract infections, and elevated creatine kinase were less prevalent in the ANGPTL3i group compared to PCSK9i (p > 0.05 for all). Other adverse clinical events were not significantly different between the groups ( *Table 2* ).

*Risk of bias assessment*

The assessment of risk of bias in the included studies using RoB2 for RCTs showed that most studies had moderate to high quality level in defining objectives and the main outcomes ( *Tables S4* ). Also, there was no evidence for publication bias as evaluated by the Egger's test for our findings.

## DISCUSSION

HoFH remains underdiagnosed and often identified too late, leading to suboptimal treatment despite the availability of several LLTs for reducing LDL-C [2, 34]. Also, guideline-recommended LDL-C targets are rarely achieved in these patients, largely due to the heterogeneous nature of the condition, which results from its diverse genetic and phenotypic presentations. Consequently, achieving optimal LDL-C levels is challenging, and newer therapies are typically added to existing treatments rather than replacing them. This practice complicates accurate evaluation of the individual efficacy of new therapies, as issues of external validity and generalizability arise from the wide variety of background treatments [1, 35, 36]. To our knowledge, this is the first meta-analysis that compares the efficacy and safety of PCSK9i and ANGPTL3i in HoFH patients. The results of our meta-analysis, which included 12 RCTs involving 392 early adult patients with HoFH and a median follow-up of 6 months, demonstrate a greater reduction in the lipid profile (TC, LDL-C, TG) and lipoproteins such as ApoB and Lp(a) in patients treated with ANGPTL3i compared to those receiving PCSK9i. Conversely, HDL-C showed a slightly greater increase in the PCSK9i groups, while Apo A levels remained unaffected in both treatment groups.

PCSK9 monoclonal antibody therapy (evolocumab or alirocumab, at approved doses for HoFH) has shown significant efficacy in reducing LDL-C levels for many patients with HoFH [22, 23, 24, 25, 26, 25, 37, 38]. However, the extent of LDL-C reduction can vary widely depending on the activity of the LDL receptor (LDLR), as well as individual genetic factors influencing response to treatment. Pharmacogenetic profiling may help predict the effectiveness of these therapies, and in some cases, the treatment response is best assessed through a trial of different therapeutic approaches [1, 2, 35]. Based on the 2023 European Atherosclerosis Society Consensus Statement on HoFH, if patients show continue [1, 7]. This variability underscores the importance of personalized treatment strategies for achieving optimal lipid control in HoFH patients. On the other hand, ANGPTL3 monoclonal antibody, targets angiopoietin-like protein 3, which plays an important role in regulating lipid-lipoprotein metabolism. Licensed for patients with HoFH aged [?]12 years, evinacumab gained approval based on results from the Phase 3 ELIPSE HoFH trial [1, 29]. Importantly, response to evinacumab was not dependent on LDL receptor (LDLR) genotype, with similar outcomes in patients with bi-allelic null variants or those with predicted residual LDL receptor function. Despite the difference in the pharmacokinetics of these two medications, at the end of the follow-up period, no significant differences were found between the treated groups in terms of the prevalence of treatment-emergent adverse events or treatment discontinuation.

The age-based subgroup analysis was of interest. It revealed a significantly greater reduction in mean LDL-C in adults compared to children, only in the PCSK9i resulted patients but not in the ANGPTL3i ones (p = 0.22). While the exact mechanism behind such differences remains incompletely understood, we hypothesize that the higher baseline LDL-C levels in the pediatric cohorts treated with PCSK9 inhibitors, compared to patients treated with ANGPTL3 inhibitors, may explain the difference in the age related treatment effect. The genotypic findings from our meta-analysis suggest a plausible higher reduction in LDL receptor (LDLR) activity, given that the cohort was relatively young and presented with markedly elevated LDL-C levels at baseline, potentially reflecting significant LDLR dysfunction. Furthermore, patients with baseline LDL-C levels greater than 13 mmol/L (500 mg/dL) did not achieve consistent lipid-lowering effects with PCSK9i, in contrast to those with lower baseline LDL-C levels (<13 mmol/L or <500 mg/dL), thus further supporting the hypothesis of LDLR impairment. In summary, the variability in responses to ANGPTL3i and the apparent discrepancies compared to other studies may be attributable to the LDLR genotype of the patient population [26, 27, 33, 35, 39, 40].

*Strength and limitations:*

Our meta-analysis highlights the efficacy and safety of new lipid-lowering therapies (ANGPTL3i and PSCK9i) in patients with HoFH, one of the most challenging forms of dyslipidemia. Due to suboptimal treatment, HoFH patients remain carrying high risk for ASCVD, contributing to a significant burden of CV outcomes and premature mortality.

However, our meta-analysis has some limitations. Moderate heterogeneity was noted in some of the analyses, although we applied a random-effects model to reduce its impact. The trials included were single-arm, which precluded direct comparisons. Nonetheless, the sub-analysis, using mean differences with inverse variance, refuted any impact of the variations in sample size or age on the results. The available data were insufficient to draw definitive conclusions regarding the effectiveness and safety of the two new drug classes, particularly in the subgroups based on genetic mutations, primarily due to the limited number of trials. Future studies are crucial to assess LDL-C response in relation to genetic mutations, which should provide more precise and individualized treatment strategies for this patient population.

*Conclusions:* This meta-analysis showed that PCSK9 inhibitors have lower efficacy in reducing LDL-C levels in HoFH patients compared to ANGPTL3 inhibitors, particularly in children. Further clinical trials are needed to compare the effectiveness of the two treatments across different functional variations of LDL-C receptors in HoFH patients.

*Conflict of interest:* Maciej Banach: speakers bureau: Amgen, Daiichi Sankyo, KRKA, Polpharma, Mylan/Viatris, Novartis; all other authors do not declare any conflict of interest in relation to the results of this paper.

Maciej Banach

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**FIGURE LEGENDS:**

**Figure 1.** Summary mean change of lipid profile

**Figure 2.** Graphical abstract

**TABLE LEGENDS:**

**Table 1.** Main characteristics of studies included in the present meta-analysis.

**Table 2.** The prevalence of adverse events among patients treated with PCSK9 and ANGPTL3 inhibitors.

**SUPPLEMENTARY DATA:**

**Table S1.** PECOS model.

**Table S2.** Literature search strategy.

**Table S3. Main characteristics of patients enrolled in included studies.**

**Table S4.** Assessment of risk of bias in the included studies using RoB2 for RCTs studies.

**Figure S1** . Flow-chart of trials included in the meta-analysis.

**Figure S2** . Summary baseline of lipids and lipoproteins in PCSK9i compared to ANGPTL3i

**Figure S3.** Mean changes of lipid profile in PCSK9i compared to ANGPTL3i: A) TC; B) LDL-C **Figure S4.** Mean changes of lipid profile in PCSK9i compared to ANGPTL3i: A) HDL-C; B) TG

**Figure S45** Mean change of lipoproteins in PCSK9i compared to ANGPTL3i: A) Lp (a); B) Apo B; C) Apo A

**Figure S6.** Mean change of LDL-C in PCSK9i compared to ANGPTL3i in different age: A) Adult; B) Children

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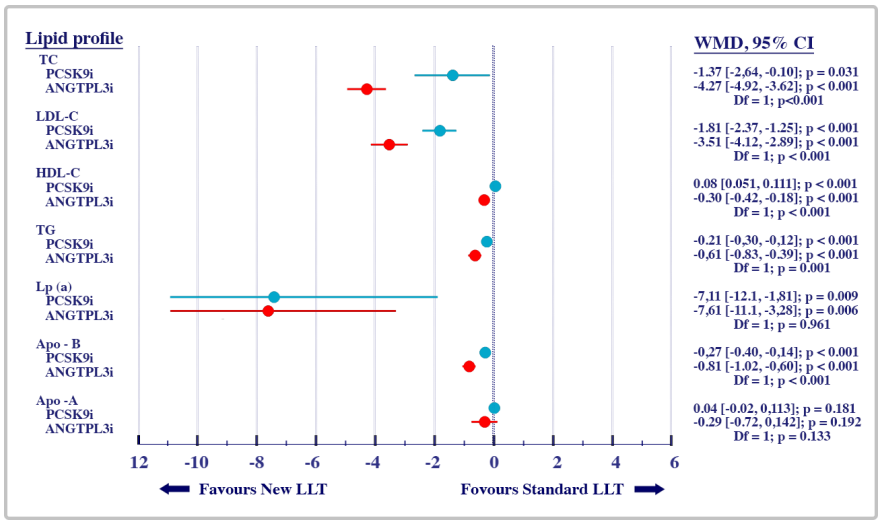


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