A Systematic Review and Meta-Analysis of Therapeutic Efficacy and Safety of Alirocumab and Evolocumab on Familial Hypercholesterolemia

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Objectives. The aim of this study was to provide the first study to systematically analyze the efficacy and safety of PCSK9-mAbs in the treatment of familial hypercholesterolemia (FH).

Methods. A computer was used to search the electronic Cochrane Library, PubMed/MEDLINE, and Embase databases for clinical trials using the following search terms: “AMG 145”, “evolocumab”, “SAR236553/REGN727”, “alirocumab”, “RG7652”, “LY3015014”, “RN316/bococizumab”, “PCSK9”, and “familial hypercholesterolemia” up to November 2020. Study quality was assessed with the Cochrane Collaboration’s tool, and publication bias was evaluated by a contour-enhanced funnel plot and the Harbord modification of the Egger test. After obtaining the data, a meta-analysis was performed using R software, version 4.0.3.

Results. A meta-analysis was performed on 7 clinical trials (926 total patients). The results showed that PCSK9-mAbs reduced the LDL-C level by the greatest margin, WMD $-49.14\%$, 95% CI: $-55.81$ to $-42.47\%$, on FH versus control groups. PCSK9-mAbs also significantly reduced lipoprotein (a) (Lp (a)), total cholesterol (TC), triglycerides (TG), apolipoprotein-B (Apo-B), and non-high-density lipoprotein cholesterol (non-HDL-C) levels and increased HDL-C and apolipoprotein-A1 (Apo-A1) levels of beneficial lipoproteins. Moreover, no significant difference was found between PCSK9-mAbs treatment and placebo in common adverse events, serious events, and laboratory adverse events.

Conclusion. PCSK9-mAbs significantly decreased LDL-C and other lipid levels with satisfactory safety and tolerability in FH treatment.

1. Introduction

Familial hypercholesterolemia (FH) is a common genetic disorder that causes high low-density lipoprotein cholesterol (LDL-C) level from birth, which causes atherosclerotic plaque deposition in the arteries and a markedly increased risk of coronary heart disease (CHD) at a young age [1]. In FH, the most common defect is loss-of-function mutations in LDL receptor alleles. Other more uncommon causes of FH are defects in apolipoprotein B (ApoB) and proprotein convertase subtilisin/kexin type 9 serine (PCSK9) [2]. FH includes homozygous and heterozygous types that have different symptoms, risks, and treatments. The incidence of FH is approximately 1 in 200–500 individuals and confers a significant risk for premature cardiovascular disease (CVD) [3]. Study has reported that the risk of premature CHD is elevated approximately 20-fold in young untreated heterozygous FH men and that homozygous FH patients typically develop CHD by the second decade of life [4].

Over the past decades, lipid-lowering drugs such as stains, ezetimibe, extended-release niacin formulations, and newer bile acid sequestrants have substantially improved
the treatment of FH patients. However, it has been clinically
observed that even if more than 50% of FH patients take
high-dose statins orally, many patients still do not achieve
desirable LDL cholesterol concentrations, and a high risk
of CVD remains [5]. PCSK9, a major regulator of LDL-C
levels, binds to the LDL receptor (LDLR) and is subsequently
internalized by the receptor to enhance LDL-C degradation
in endo-/lysosomal vesicles in the liver [6]. Phase 1 and 2 tri-
als of PCSK9-mAbs have shown that the level of LDL cho-
lesterol is further reduced by 55-60% when they are added
to existing lipid-lowering treatments, for example, stains
alone or stains combined with ezetimibe. Alirocumab/
SAR236553/REGN727 and evolocumab/AMG145 are classic
human PCSK9-mAbs. In recent years, studies have demon-
strated that RG7652 [7], LY3015014 [8], and bococizum-
bab/RN316 [9] are e

eff

ective for altering the lipidome of
plasma and lipoprotein fractions. However, these drug-
related clinical studies were terminated.

Clinical trials have proven that PCSK9-mAbs (alirocu-
mab and evolocumab) decrease the plasma LDL-C level in
FH patients. Other lipids and lipoproteins, such as lipopro-
tin (a) (Lp(a)), total cholesterol (TC), triglycerides (TG),
apolipoprotein-B (Apo-B), high-density lipoprotein chole-
sterol (HDL-C), and apolipoprotein-A1 (Apo-A1), can also
benefit [10]. However, no report has comprehensively pin-
pointed the applicable targets of PCSK9-mAb-FH patients
with sufficient clinical outcomes. To confirm the efficacy
and safety of PCSK9-mAbs in FH patients, a total of 7 arti-
cles (926 patients) were assessed in this meta-analysis.

2. Methods

2.1. Literature Search. We followed the methods of our pre-
vious study described [11]. In general, we obtained individ-
ual participant data from studies identified through
systematic searches of the published literature performed
using the Cochrane Library, PubMed/MEDLINE, and
Embase databases (the following search terms were used:
“AMG 145”, “evolocumab”, “SAR236553/REGN727”, “aliro-
cumab”, “RG7652”, “LY3015014”, “RN316/bococizumab”,
“PCSK9”, and “familial hypercholesterolemia” clinical trial)
up to November 2020. We obtained articles in peer-
reviewed journals for electronic searches. Additional data,
especially original data not identified in the electronic data-
bases, were collected from other data resources, and we also
performed an additional search of the references of the
retrieved studies. Notably, we obtained original data by con-
tacting the corresponding authors when the data were not
reported in the identified published articles.

2.2. Selection of Studies for Inclusion in the Review. Cohort
studies were included if they met the following criteria: (1)
type of study: randomized controlled trials (RCTs); (2) types
of participants: FH diagnosis in accordance with clinical cri-
teria or DNA-based analyses; (3) type of interventions:
patients received PCSK9-mAbs; and (4) safety and efficacy
outcomes of PCSK9-mAbs. The exclusion criteria were as
follows: (1) duplicate reports describing the same cohort;
(2) certain publication types, such as conference abstracts,
letters, comments, case reports, and editorials; (3) repeated
patient population for long-term research on the efficacy
and safety of PCSK9 inhibitors; (4) mixed with other
diseases; (5) clinical or outcome data not reported.

2.3. Data Extraction. All studies retrieved by the search strat-
egy were independently screened by 2 reviewers (XYG and
TTZ). The initial prescreening was performed by reading
the titles and abstracts to select relevant studies for further
data extraction. Secondary selection was conducted by com-
prehensively reviewing the full text of all initially identified
articles to determine whether the necessary information
was reported. Basic information was extracted as follows:
| Author          | Year | Patients   | Mean age (y) | Number (P/C) | PCSK9-mAbs                  | Control   | Drug regimen                                      | Time                   | Area                                                                 | Duration |
|-----------------|------|------------|--------------|--------------|-----------------------------|-----------|---------------------------------------------------|------------------------|----------------------------------------------------------------------|----------|
| Raal et al. [16]| 2015 | heFH       | 51           | 220/109      | Evolocumab                  | Placebo   | 140 mg every 2 weeks, 420 mg monthly              | Feb 7 to Dec 19, 2013 | Australia, Asia, Europe, New Zealand, North America, and South Africa | 12 weeks |
| Raal et al. [17]| 2012 | heFH       | 51           | 111/56       | Evolocumab (AMG 145)        | Placebo   | 350 mg-420 mg, every 4 weeks                      | Aug 2011 to Feb 2012  | North America, Western Europe, Hong Kong, Singapore, and South Africa | 12 weeks |
| Ginsberg et al. [15] | 2016 | heFH       | 50.6         | 72/35        | Alirocumab                  | Placebo   | 150 mg, every 2 weeks                             | June 2012 to Jan 2015 | Canada, the United States, the Netherlands, Russia, and South Africa | 78 weeks |
| Stein et al. [14] | 2012 | heFH       | 53.4         | 62/15        | Alirocumab (REGN727)        | Placebo   | 150 mg, 200 mg, and 300 mg, every 4 weeks; then 150 mg every 2 weeks | Jan 18, 2011, to Nov 7, 2011 | USA and Canada                                                                       | 12 weeks |
| Moriarty et al. [13] | 2016 | heFH       | 58.7         | 41/21        | Alirocumab                  | Placebo   | 150 mg, every 2 weeks                             | Mar 2015 to Sep 2015  | United States and Germany                                                                                                           | 18 weeks |
| Raal et al. (2) [18] | 2015 | hoFH       | 31           | 33/16        | Evolocumab                  | Placebo   | 420 mg, every 4 weeks                             | Feb 17, 2013, to Jan 31, 2014 | North America, Europe, Middle East, and South Africa                                                                  | 12 weeks |
| Stein et al. (2) [19] | 2012 | heFH and non-FH | 45            | 101/32       | Alirocumab                  | Placebo   | Single-dose study: 50, 100, 150, and 250 mg; multiple-dose study: 50, 100, or 150 mg on days 1, 29, and 43 | Nov 2009 to May 2011 | Kansas, Miramar, Florida                                                                                                             | 148 days |
author, year, patient number, mean age (y) at baseline, the type of PCSK9-mAbs, control, drug regimen, duration, study time, and area. Then, we extracted the corresponding mean differences, 95% CI or LS mean percent change, and SE from baseline of each lipid items, including LDL-C, HDL-C, non-HDL-C, TC, Apo-B and Apo-A1, TG, and Lp(a), as the primary outcomes. Safety endpoints covering the common adverse events, serious events, and laboratory adverse events were compared between the treatment and control groups.

2.4. Quality Evaluation. The literature quality evaluation used the Cochrane risk assessment form to conduct risk assessment on the included studies as described by "McKenzie et al." [12]. The assessment content includes (1) whether the random method is correct; (2) whether the allocation is hidden; (3) whether the implementer and participants are blinded; (4) whether the result analysis applies the blinding method; whether the data results are fully reported; (5) whether there is selective reporting; and whether there are other biases. According to specific circumstances, the risk assessment results are divided into three situations: high, low, and unclear. High-risk assessment research may lead to unsound analysis results, which are analyzed in sensitivity analysis and subgroup analysis.

2.5. Appraisal of the Risk of Bias of the Included Studies. Potential publication bias was evaluated by visually contour-enhanced funnel plots and Egger’s test. According to the Egger methods for evaluating publication bias, a two-sided $p$ value of 0.10 or less was regarded as significant.

2.6. Sensitivity Analysis. When substantial heterogeneity was noted between trials, leave-one-out sensitivity analysis was used, which means removing one study each time and repeating the analysis to determine whether exclusion of any one of the included studies altered the results.

2.7. Statistical Analysis. Statistical analyses were performed using R software, version 4.0.3 (R Foundation). The $\chi^2$ statistic and independent-samples $T$-tests were used to assess differences in the baseline characteristics of the two groups. The risk ratio (RR) and weighted mean difference (WMD) were calculated and presented with the 95% confidence interval (CI) for summary estimates. Due to the heterogeneity among the included studies, appropriate statistical models were selected to ensure that the statistical data were estimated correctly. Statistical heterogeneity between studies was assessed using the $\chi^2$ test, with a $p$ value of less than 0.1 considered to indicate statistical significance, and heterogeneity was quantified using the inconsistency ($I^2$) statistic. The $I^2$ statistic describes the percentage of total variation across studies due to significant heterogeneity rather than random chance. An $I^2$ statistic greater than 50% suggests considerable heterogeneity among the studies. Publication bias was assessed using contour-enhanced funnel plots. Because the visual interpretation of funnel plot asymmetry is inherently subjective, we also formally tested funnel plot asymmetry using the Harbord modification of Egger’s test. Statistical significance was set at a $p$ value < 0.05.
Figure 3: Continued.
Figure 3: Appraisal of the risk of bias of the included studies: (a) any adverse events; (b) serious adverse events; (c) leading to treatment discontinuation; (d) adjudicated cardiovascular events; (e) nervous system disorders; (f) creatine kinase (CK ≥ 3 × ULN); (g) headache; (h) nasopharyngitis; (i) abnormal liver function risk (AST/ALT ≥ 3 × ULN); (j) injection site reactions.

3. Results

3.1. Study Selection and Characteristics. Literature search results and characteristics were initially obtained from 993 articles, and there were 55 clinical studies. Eighteen papers were removed after reviewing the titles and abstracts. Then, the full text of each of the remaining 37 articles was retrieved for further review to determine whether they met the predetermined criteria. Finally, 7 papers were identified and included in the present study (Figure 1). As a result, 7 studies encompassing a total of 926 patients were selected [13–19]. Among them, 3 trials used evolocumab (AMG 145), and 4 studies used alirocumab (SAR236553/-REGN727) treatment. Baseline characteristics were detailed, giving substantially similar basic values between PCSK9-mAbs and controls. The mean age of the subjects ranged from 31 to 59 years old. All trials were published between 2012 and 2016 with a follow-up period ranging from 8 to 78 weeks (Table 1) and a low risk of bias (Figure 2).

3.2. Bias Assessment and Consistency Test. Funnel plots were used to investigate the presence of small-study effects and publication bias. Figure 3 shows the contour-enhanced funnel plots and the Harbord modification of the Egger test of the studies included in this meta-analysis for adverse events, such as common adverse events, serious adverse events, and laboratory adverse events. There was no apparent asymmetry for the studies examining PCSK9-mAbs versus placebo for most of the adverse events, other than leading to treatment discontinuation and creatine kinase level (CK ≥ 3 × upper limit of normal (ULN)).

3.3. Efficacy Outcomes of PCSK9-mAbs. We could see from Figure 4 that PCSK9-mAbs markedly decreased the LDL-C level by -49.14%, 95% CI: -55.81 to -42.47%, I²: 99%, p < 0.01 (Figure 4(a)), and increased the level of HDL-C by 6.41%, 95% CI: 4.09 to 8.73%, I²: 95%, p < 0.01 (Figure 4(b)), and Apo-A1 by 8.27, 95% CI: 3.38 to 13.16%, I²: 99%, p < 0.01 (Figure 4(c)). They also decreased the level of Apo-B by -38.09%, 95% CI: -45.03 to 31.16%, I²: 98%, p < 0.01 (Figure 4(d)); non-HDL-C by -46.26%, 95% CI: -53.45 to 39.06%, I²: 93%, p < 0.01 (Figure 4(e)); TC by -36.47%, 95% CI: -42.09 to 28.84%, I²: 97%, p < 0.01 (Figure 4(f)); TG by -10.26%, 95% CI: -18.68 to -1.84%, I²: 95%, p < 0.01 (Figure 4(g)); and Lp(a) by -17.65%, 95% CI: -24.75 to -10.55%, I²: 98%, p < 0.01 (Figure 4(h)).

As a lipid outcome of evolocumab, a significant reduction in LDL-C level was achieved (WMD: -49.45%, 95% CI: -57.04 to -41.85%, I²: 99%, p < 0.01, Figure 4(a)). In addition, HDL-C level obviously increased by 5.94% (95% CI: 3.11 to 8.76%, I²: 97%, p < 0.01, Figure 4(b)), and Apo-A1 level increased by 5.20% (95% CI: -1.66 to 12.06%, I²: 100%, p < 0.01, Figure 4(c)). Furthermore, Apo-B level obviously decreased by -40.12% (95% CI: -46.47 to -33.78%, I²: 99%, p < 0.01, Figure 4(d)), non-HDL-C level by -54.21% (95% CI: -55.48 to -52.94%, I²: 76%, p = 0.043, Figure 4(e)), TC level by -40.30% (95% CI: -41.08 to 39.52%, I²: 97%, p < 0.01, Figure 4(f)), TG level by -14.07% (95% CI: -19.74 to -8.41%, I²: 97%, p < 0.01, Figure 4(g)), and Lp(a) level by -22.56% (95% CI: -30.33 to -14.78%, I²: 99%, p < 0.01, Figure 4(h)) versus placebo.

As a lipid outcome of alirocumab, a significant reduction in LDL-C level was achieved (mean reduction: −49.10%, 95% CI: −57.91 to −40.28%, I²: 97%, p < 0.01, Figure 4(a)). In addition, HDL-C level obviously increased by 7.12% (95% CI: 2.83 to 11.42%, I²: 93%, p < 0.01, Figure 4(b)) and Apo-A1 level increased by 11.43% (95% CI: 6.19 to 16.66%, I²: 93%, p < 0.01, Figure 4(c)). Moreover, Apo-B level obviously decreased by -36.38% (95% CI: -43.75 to -29.01%, I²: 97%, p < 0.01, Figure 4(d)), non-HDL-C level by -40.79% (95% CI: -47.00 to -34.58%, I²: 95%, p < 0.01, Figure 4(e)), TC level by -33.80% (95% CI: -40.24 to 27.36%, I²: 97%, p < 0.01, Figure 4(f)), TG level by -5.68% (95% CI: -5.93 to -5.43%, I²: 0%, p = 0.968, Figure 4(g)), and Lp(a) level by -12.89% (95% CI: -20.17 to -5.61%, I²: 94%, p < 0.01, Figure 4(h)) versus placebo.

3.4. Safety Outcomes of PCSK9-mAbs. We compared the safety endpoints covering the common adverse events, serious events, and laboratory adverse events between the PCSK9-mAbs and control groups and found that the overall
Figure 4: Continued.
Figure 4: Forest plots depicting the effect of PCSK9 monoclonal antibody on FH; (a) on LDL-C; (b) on HDL-C; (c) on Apo-A1; (d) on Apo-B; (e) on non-HDL-C; (f) on TC; (g) on TG; (h) on Lp(a).
| Study Events | Study Events | Risk ratio | Weight (fixed) | Weight (random) |
|--------------|--------------|------------|----------------|----------------|
| Frederick J. Raal 2015 | 61 | 61 | 1.30 [0.92; 1.85] | 21.2% | 16.7% |
| Frederick J. Raal 2012 | 32 | 32 | 0.99 [0.72; 1.39] | 22.4% | 19.5% |
| Henry N. Ginsberg 2016 | 51 | 51 | 0.89 [0.71; 1.11] | 25.8% | 24.8% |
| Evau A. Snit 2016 | 12 | 12 | 1.25 [0.76; 2.06] | 6.4% | 10.8% |
| Patrick M. Moriarty 2016 | 31 | 31 | 0.99 [0.74; 1.33] | 14.5% | 19.9% |
| Frederick J. Raal (2) 2015 | 12 | 12 | 0.58 [0.32; 1.05] | 9.2% | 8.5% |
| Evau A. Snit (2) 2012 | 10 | 10 | 0.81 [0.60; 1.29] | 9.5% | 5.5% |

**Random effect model**

| Study Events | Study Events | Risk ratio | Weight (fixed) | Weight (random) |
|--------------|--------------|------------|----------------|----------------|
| Frederick J. Raal (2) 2015 | 342 | 342 | 1.05 [0.91; 1.21] | 100.0% | -- |
| Henry N. Ginsberg 2016 | 15 | 15 | 1.00 [0.82; 1.22] | -- | 100.0% |

**Heterogeneity**: $\tau^2 = 0.0273$, $p = 0.10$

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Figure 5: Continued.
Figure 5: Forest plot depicting the adverse event rates of PCSK9 monoclonal antibody on FH compared with placebo controls on adverse events, serious events, and laboratory adverse events: (a) any adverse events; (b) serious adverse events; (c) leading to treatment discontinuation; (d) adjudicated cardiovascular events; (e) nervous system disorders; (f) creatine kinase (CK ≥ 3 × ULN); (g) headache; (h) nasopharyngitis; (i) abnormal liver function risk (AST/ALT ≥ 3 × ULN); (j) injection site reactions.

Table 2: Prespecified safety end points. No statistical differences between the PCSK9-mAbs and control groups.

| Pre-specified Safety endpoints | PCSK9-mAbs | Control | Rate (%) | No. of patients/objects | Rate (%) | No. of patients/objects |
|-------------------------------|------------|---------|----------|-------------------------|----------|-------------------------|
| Any adverse events           | 209/342    | 0.611111| 119/203  | 0.5862069               | 0.33     | 0.314                   |
| Serious adverse events       | 13/256     | 0.0507813| 4/126    | 0.031746                | 0.72     | 0.287                   |
| Nervous system disorders     | 13/162     | 0.0802469| 3/87     | 0.0348288               | 1.972    | 0.127                   |
| Injection site reactions     | 26/398     | 0.0653266| 8/203    | 0.0394089               | 1.692    | 0.131                   |
| Leading to treatment discontinuation | 10/257 | 0.0446429| 4/128    | 0.03125                | 0.143    | 0.477                   |
| Nasopharyngitis              | 31/310     | 0.1     | 10/153   | 0.0653595               | 1.523    | 0.144                   |
| Back pain                    | 7/151      | 0.0463576| 2/75     | 0.0266667               | 0.508    | 0.377                   |
| Headache                     | 13/277     | 0.0469314| 7/137    | 0.0510949               | 0.035    | 0.513                   |
| ALT, AST, or both ≥ 3 × ULN  | 8/216      | 0.037037 | 2/107    | 0.0186916               | 0.803    | 0.3                     |
| Positively adjudicated cardiovascular events | 14/239 | 0.0585774| 7/125    | 0.056                   | 0.01     | 0.563                   |
| Creatinine kinase ≥ 3 × ULN  | 10/248     | 0.0403226| 2/128    | 0.0169422               | 1.667    | 0.164                   |
Study | Mean difference | MD | 95%-CI | Fixed effect model
--- | --- | --- | --- | ---
Omitting frederick J raal 2015 | -51.08 | [-51.90; -50.25] | 
Omitting frederick raal 2012 | -52.82 | [-53.64; -51.99] | 
Omitting henry N. ginsberg 2016 | -56.35 | [-57.05; -55.65] | 
Omitting evan A stein 2012 | -53.99 | [-54.66; -53.33] | 
Omitting patrick M. moriarty 2016 | -54.48 | [-55.15; -53.81] | 
Omitting frederick J raal (2) 2015 | -54.65 | [-55.31; -53.99] | 
Omitting evan A stein (2) 2012 | -54.11 | [-54.77; -53.45] | 
Omitting frederick raal 2012 | -56.35 | [-57.05; -55.65] | 
Omitting henry N. ginsberg 2016 | -53.99 | [-54.66; -53.33] | 
Omitting evan A stein 2012 | -54.48 | [-55.15; -53.81] | 
Omitting patrick M. moriarty 2016 | -54.65 | [-55.31; -53.99] | 
Omitting frederick J raal (2) 2015 | -54.11 | [-54.77; -53.45] | 

Fixed effect model

Study | Mean difference | MD | 95%-CI | Fixed effect model
--- | --- | --- | --- | ---
Omitting frederick J raal 2015 | 5.87 | [5.33; 6.40] | 
Omitting frederick raal 2012 | 7.82 | [7.35; 8.29] | 
Omitting henry N. ginsberg 2016 | 8.21 | [7.79; 8.63] | 
Omitting evan A stein 2012 | 7.45 | [7.05; 7.84] | 
Omitting patrick M. moriarty 2016 | 7.50 | [7.10; 7.89] | 
Omitting frederick J raal (2) 2015 | 7.63 | [7.24; 8.02] | 

Fixed effect model

Study | Mean difference | MD | 95%-CI | Fixed effect model
--- | --- | --- | --- | ---
Omitting frederick J raal 2015 | 3.27 | [2.73; 3.81] | 
Omitting frederick raal 2012 | 9.06 | [8.52; 9.60] | 
Omitting henry N. ginsberg 2016 | 5.43 | [5.03; 5.84] | 
Omitting evan A stein 2012 | 5.55 | [5.14; 5.96] | 
Omitting patrick M. moriarty 2016 | 5.74 | [5.34; 6.14] | 

Fixed effect model

Study | Mean difference | MD | 95%-CI | Fixed effect model
--- | --- | --- | --- | ---
Omitting frederick J raal 2015 | -40.20 | [-40.92; -39.48] | 
Omitting frederick raal 2012 | -44.26 | [-44.84; -43.67] | 
Omitting henry N. ginsberg 2016 | -46.81 | [-47.34; -46.27] | 
Omitting evan A stein 2012 | -45.25 | [-45.76; -44.73] | 
Omitting patrick M. moriarty 2016 | -45.14 | [-45.65; -44.64] | 
Omitting frederick J raal (2) 2015 | -44.78 | [-45.28; -44.28] | 

Fixed effect model

Study | Mean difference | MD | 95%-CI | Fixed effect model
--- | --- | --- | --- | ---
Omitting frederick J raal 2015 | -47.48 | [-48.28; -46.67] | 
Omitting frederick raal 2012 | -50.85 | [-51.48; -50.23] | 
Omitting henry N. ginsberg 2016 | -53.57 | [-54.14; -53.00] | 
Omitting evan A stein 2012 | -51.70 | [-52.24; -51.15] | 
Omitting patrick M. moriarty 2016 | -51.98 | [-52.53; -51.44] | 

Fixed effect model

Study | Mean difference | MD | 95%-CI | Fixed effect model
--- | --- | --- | --- | ---
Omitting frederick J raal 2015 | -31.51 | [-32.57; -30.45] | 
Omitting henry N. ginsberg 2016 | -39.71 | [-40.42; -39.00] | 
Omitting evan A stein 2012 | -37.35 | [-38.00; -36.71] | 
Omitting patrick M. moriarty 2016 | -37.16 | [-37.81; -36.50] | 

Fixed effect model

Figure 6: Continued.
incidence of common adverse events (RR: 1.00, 95% CI: 0.82 to 1.22, $I^2$: 44%), serious adverse events (RR: 1.18, 95% CI: 0.39 to 3.54, $I^2$: 0%, $p = 0.40$), and leading to treatment discontinuation (RR: 1.23, 95% CI: 0.40 to 3.84, $I^2$: 0%, $p = 0.95$) implied no obvious differences versus placebo. No significant heterogeneity was found in positively adjudicated cardiovascular events by RR: 0.88, 95% CI: 0.28 to 2.80, $I^2$: 22%, $p = 0.28$; nervous system disorders by RR: 1.95, 95% CI: 0.52 to 7.28, $I^2$: 14%, $p = 0.31$; creatine kinase (CK ≥ 3 × ULN) by RR: 1.70, 95% CI: 0.47 to 6.20, $I^2$: 0%, $p = 0.76$; headache by RR: 0.88, 95% CI: 0.35 to 2.20, $I^2$: 0%, $p = 0.55$; nasopharyngitis by RR: 1.38, 95% CI: 0.71 to 2.68, $I^2$: 0%, $p = 0.93$; abnormal liver function risk (AST/ALT ≥ 3 × ULN) in patients by RR: 1.60, 95% CI: 0.39 to 6.49, $I^2$: 0%, $p = 0.86$; and injection site reactions by RR: 1.77, 95% CI: 0.83 to 3.77, $I^2$: 0%, $p = 0.60$, versus placebo (Figure 5).

Moreover, an additional table that describes the safety events of interest, common adverse events, and laboratory adverse events of PCSK9-mAbs was included, and we found no significant differences between the PCSK9-mAbs and control groups. A chi-square ($\chi^2$) statistic was used to assess the magnitude of heterogeneity, and a $p$ value < 0.05 was considered to be statistically significant (Table 2).

3.5. Sensitivity Analysis. To explain the high heterogeneity observed among all efficacy outcomes, we performed leave-one-out sensitivity analysis among the studies. We found that the statistical significance or nonsignificance of the differences between groups was not altered. This suggested that none of the included studies individually changed the overall result (Figure 6). Moreover, there was also no change in safety outcomes (Figure 7).

4. Discussion

To the best of our knowledge, this is the first meta-analysis using sufficient clinical outcomes to systematically analyze the efficacy and safety of PCSK9-mAbs in the treatment of FH patients. In the present analysis, a total of 7 studies encompassing 926 patients with FH were included. The main aim is to solve whether PCSK9-mAbs treatment can reduce the levels of lipids of FH patients with satisfactory safety and tolerability.

FH is an inherited disease due to a genetic mutation and is not caused by the external environment or improper lifestyle. As mentioned before, FH includes two main subtypes: HeFH and homozygous FH. They are different in symptoms, risks, and treatments. In genetics, HeFH is caused by a pathogenic variant in one allele, while biallelic mutations in one of the known genes or compound heterozygosity for two different mutations in the same or different candidate genes cause homozygous FH. HeFH affects between one in 250 and one in 300 people worldwide, and the prevalence of homozygous FH may be 1 in 160,000 [20]. The risk of premature CHD in heterozygous FH is elevated approximately 20-fold [4], and homozygous FH patients develop CHD early by the second decade of life. In homozygous FH, valvular and supravalvular aortic stenosis induced by lipid deposition has also been reported, whereas rarely in HeFH [21]. To date, 12 meta-analysis studies have analyzed the efficacy and safety of PCSK9-mAbs in hypercholesterolemia [9, 22–32]. Among these studies, there were two in FH patients. However, one report studied the role and safety of evolocumab but did not include alirocumab [33]. In another study, although the role and safety of PCSK9-mAbs, including evolocumab and alirocumab, were discussed, the patients with
Study | Risk ratio | RR | 95%-Cl
--- | --- | --- | ---
Omitting frederick J raal 2015 | 0.98 | 0.84; 1.14
Omitting frederick raal 2012 | 1.06 | 0.91; 1.25
Omitting henry N.ginsberg 2016 | 1.10 | 0.93; 1.31
Omitting evan A.stein 2012 | 1.03 | 0.89; 1.20
Omitting patrick M.moriarity 2016 | 1.06 | 0.90; 1.24
Omitting frederick J raal (2) 2015 | 1.09 | 0.94; 1.27
Omitting evan A.stein (2) 2012 | 1.01 | 0.88; 1.16

Fixed effect model 0.8 1 1.25 1.05 [0.91; 1.21]

Study | Risk ratio | RR | 95%-Cl
--- | --- | --- | ---
Omitting frederick J raal 2015 | 2.11 | 0.55; 8.11
Omitting henry N.ginsberg 2016 | 0.88 | 0.27; 2.88
Omitting patrick M.moriarity 2016 | 1.87 | 0.47; 7.40
Omitting frederick J raal (2) 2015 | 1.50 | 0.53; 4.24

Fixed effect model 0.2 0.5 1 2 5 1.50 [0.53; 4.24]

Study | Risk ratio | RR | 95%-Cl
--- | --- | --- | ---
Omitting frederick raal 2012 | 1.32 | 0.36; 4.77
Omitting henry N.ginsberg 2016 | 1.31 | 0.36; 4.77
Omitting patrick M.moriarity 2016 | 1.24 | 0.40; 3.84
Omitting frederick J raal (2) 2015 | 1.24 | 0.40; 3.84

Fixed effect model 0.2 0.5 1 2 5 1.24 [0.40; 3.84]

Study | Risk ratio | RR | 95%-Cl
--- | --- | --- | ---
Omitting frederick J raal 2015 | 0.93 | 0.39; 2.22
Omitting henry N.ginsberg 2016 | 0.64 | 0.25; 1.63
Omitting evan A.stein 2012 | 2.02 | 0.52; 7.97
Omitting patrick M.moriarity 2016 | 1.03 | 0.45; 2.37

Fixed effect model 0.2 0.5 1 2 10 1.03 [0.45; 2.37]

Study | Risk ratio | RR | 95%-Cl
--- | --- | --- | ---
Omitting henry N.ginsberg 2016 | 4.43 | 0.86; 22.88
Omitting evan A.stein 2012 | 1.67 | 0.48; 5.81
Omitting patrick M.moriarity 2016 | 1.67 | 0.44; 6.34
Omitting frederick J raal (2) 2015 | 2.23 | 0.73; 6.77

Fixed effect model 0.1 0.5 1 2 10 2.23 [0.73; 6.77]

Study | Risk ratio | RR | 95%-Cl
--- | --- | --- | ---
Omitting frederick J raal 2012 | 1.64 | 0.42; 6.49
Omitting henry N.ginsberg 2016 | 2.48 | 0.56; 10.97
Omitting patrick M.moriarity 2016 | 1.48 | 0.36; 6.04
Omitting frederick J raal (2) 2015 | 2.48 | 0.56; 11.06

Fixed effect model 0.1 0.5 1 2 10 1.97 [0.57; 6.79]
FH were controversial because the data extracted by the authors did not exclude the non-FH patients included in the clinical study [10]. Therefore, strictly speaking, our meta-analysis is the first study to systematically analyze the efficacy and safety of PCSK9-mAbs in the treatment of FH patients alone. In addition, we conducted a variety of sensitivity analyses for the included literature to ensure the reliability of the literature screening and results, including leave-one-out sensitivity analysis, contour-enhanced funnel plots, and the Harbord modification of Egger test. Moreover, we conducted a subgroup analysis of PCSK9-mAbs and analyzed the efficacy outcomes and safety outcomes of evolocumab and alirocumab in the treatment of FH, respectively.

In this study, we conducted a systematic evaluation of the efficacy and safety of PCSK9-mAbs in FH patients. The results of this study showed that PCSK9-mAbs reduced the level of the main research index LDL-C and also significantly reduced the levels of TG, TC, non-HDL-C, and Apo B, Lp(a) and increased the levels of HDL-C and Apo-A1, which are beneficial lipoproteins. Elevated LDL is an important pathological factor for CVD. The latest Mendelian Randomization Study Tips published by JACC based on the UK Biobank and Global Lipid Genetics Consortium (Global Lipid Genetics Consortium) demonstrated that LDL cholesterol and triglycerides induced myocardial remodeling by increasing LV mass, suggesting that they influence the development of CVD not only through atherosclerosis but also by causing adverse alterations in cardiac structure and function [34, 35]. In the present study, we showed that PCSK9-mAbs significantly reduced LDL and TG levels by -49.14% and -10.26%, respectively. The Apo-B/Apo-A1 ratio has been previously suggested to be a better risk indicator for CVD and MI than the level of lipids [36], and we demonstrated that in the PCSK9-mAbs treatment group, the level of Apo-B decreased while that of Apo-A1 increased. This result indicates that PCSK9-mAbs therapy can greatly lower the primary risk factors for heart disease with an obvious decrease in the Apo-B/Apo-A1 ratio. Recent studies have reported that Lp(a) not only serves as a "traditional"
atherosclerotic cardiovascular disease (ASCVD) risk factor but also improves the accuracy of cardiovascular risk stratification [37]. Compelling evidence from traditional epidemiological, genome-wide association, and Mendelian randomization studies has revealed that elevated plasma Lp(a) level increases the risk of acute myocardial infarction (AMI), ischemic stroke, calcific aortic valve disease, and peripheral arterial disease in non-FH patients [38]. Elevated lipoprotein (a) was found to be a significant CVD risk factor in HeFH [39], and Lp(a) level above 50 mg/dL is recently found to be an independent risk factor for calcific aortic valveopathy among HeFH patients [40]. Safety analysis demonstrated that PCSK9-mAbs showed good safety, and the incidence of common and serious adverse reactions was basically the same as that of the placebo group in addition to abnormal liver function risk.

Several limitations should be taken into consideration. First, significant heterogeneities were observed in most of the efficacy outcomes, which may be related to the patient’s baseline level, drug intervention time, the type and dose of PCSK9-mAbs, etc., but we failed to reveal the heterogeneities by dividing into subgroups or using sensitivity methods. Second, there are still a number of large-scale randomized clinical controlled studies in progress, and we should take caution in interpreting the results of the meta-analysis when combining heterogeneous data sets. Third, most of the treatment cycles included in clinical studies were between 12 and 24 weeks, and the adverse reactions that require long-term observation could not be effectively evaluated. Despite these limitations, our meta-analysis proves that PCSK9-mAbs exert significant protection from FH, including decreasing the plasma levels of LDL-C and Lp(a), TC, TG, and Apo-B and increasing the plasma levels of HDL-C and Apo-A1. Outcomes are sufficient enough to compensate our clinical guidelines. Hopefully, its long-term therapeutic efficacy, safety, and clinical outcomes should be confirmed by more RCTs.

5. Conclusion

In this review, we presented evidence from 7 published clinical trials and suggested that among 926 FH patients, PCSK9-mAbs significantly decreased the level of LDL-C and other lipids with satisfactory safety and tolerability.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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