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Latest clinical evidence about the effect of PCSK9 monoclonal antibodies in patients with familial hypercholesterolaemia: an updated meta-analysis

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Abstract

Introduction: Familial hypercholesterolaemia (FH) is the most common autosomal genetic disease of cholesterol metabolism disorder. Proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody (mAb) is a new target lipid-regulating drug related to cholesterol metabolism that has been developed in recent years. The reported rate of reduction varies widely, and comprehensive assessments of efficacy and safety are lacking. Therefore, we conducted this study to investigate the clinical effect of PCSK9 mAbs in patients with familial hypercholesterolaemia to provide a theoretical reference for clinical practice.

Material and methods: We analysed the clinical data of patients, including the percentage change in LDL-C and the incidence rates of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), from selected articles. Weighted mean differences (WMDs), risk ratios (RRs), and 95% confidence intervals (95% CIs) were calculated to compare the endpoints.

Results: The results showed that, compared with placebo, the PCSK9 mAb reduced the percentage change in LDL-C in FH patients (WMD = –45.52, 95% CI: –49.70 to –41.34, I^2 = 99.6%). In addition, there was no significant difference between the experimental and placebo groups in the incidence of TEAEs (RR = 1.03, 95% CI: 0.97 to 1.10, I^2 = 19.1%) and SAEs (RR = 1.02, 95% CI: 0.72 to 1.44, I^2 = 0.0%).

Conclusions: Overall, PSCK9 mAbs are an effective and safe method of LDL-C reduction in patients with FH. **(Endokrynol Pol 2022; 73 (1): 110–120)**

Key words: *PCSK9 mAb; alirocumab; evolocumab; familial hypercholesterolaemia; low-density lipoprotein cholesterol; meta-analysis*

Introduction

Familial hypercholesterolaemia (FH) is the most common autosomal genetic disease of cholesterol metabolism disorder [1]. In FH, plasma total cholesterol and low-density lipoprotein cholesterol (LDL-C) are extremely high, and the condition is difficult to control with drugs. Therefore, xanthoma, premature atherosclerosis, and premature coronary disease easily appear [2]. According to the difference in inheritance modes, FH can be divided into autosomal dominant inheritance and autosomal recessive inheritance [3]. The former is mainly the functional mutation of low-density lipoprotein receptor (LDLR), apolipoprotein B (ApoB), and proprotein convertase subtilisin/kexin type 9 (PCSK9), and the latter is mainly the functional mutation of low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) [4]. Genetically, FH can be divided into homozygous familial hypercholesterolaemia (HoFH) and heterozygous familial hypercholesterolaemia (HeFH). Mutations could be detected in two homologous genes of HoFH patients. Almost no receptors with normal structure and function were produced. One homologous gene of HeFH patients was mutated, and half of the receptors with normal structure and function were produced [5]. The results of several studies showed that the incidence of HeFH was 1/500∼1/200 and that of HoFH was 1/300,000∼1/160,000 in most people, while the actual incidence rates may be higher. The incidence of HeFH can reach 1/33 in people with coronary heart disease [6]. Most patients with FH are diagnosed and initiate treatment after their first coronary artery event, which leads to a poor prognosis. Early detection and intervention of FH are particularly important, but the diagnosis of FH is still seriously inadequate, and the diagnosis rate in most countries is less than 1%, which is more prominent in China [1, 2]. FH patients are commonly underdiagnosed and undertreated; thus, increasing the public awareness of FH, early recognition, and timely treatment may improve the long-term cardiovascular prognosis of FH patients and contribute to the prevention and treatment of FH.

PCSK9 is a serine protease encoded by the PCSK9 gene, which is mainly produced by the liver [7]. PCSK9 binds to LDLR on the surface of hepatocytes, which degrades LDL-R and increases plasma LDL-C levels

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[8]. PCSK9 mAb is a new target lipid-regulating drug related to cholesterol metabolism that has been developed in recent years. It can specifically block the degradation of LDLR in hepatocytes and increase the expression of LDLR on the surface of hepatocytes, thus promoting LDL-C metabolism and reducing the serum LDL-C concentration [9, 10]. Studies have shown that PCSK9 mAbs can significantly reduce LDL-C levels and cardiovascular events in patients with atherosclerotic cardiovascular diseases [11]. More than 60% of the patients who failed to meet the lipid-lowering standard of statins could reduce their LDL-C levels to below 70 mg/dL after adding PCSK9 mAb [12]. The current total anthropogenic evolocumab monoclonal antibody (mAb) and alirocumab mAb have been approved for clinical treatment. Bococizumab, another type of PCSK 9 mAb, has been studied in phase I-III clinical studies and was found to reduce both LDL-C and the incidence of cardiovascular events. In November 2016, clinical development of bococizumab was discontinued as a result of a higher incidence of anti-drug antibodies and a higher rate of injection-site reactions in the SPIRE phase III lipid-lowering programme. With the publication and update of results from several clinical trials, PCSK9 mAbs may further reduce LDL-C levels in patients in concert with existing lipid-lowering therapy, but the reported rate of reduction varies widely, and more comprehensive assessments of efficacy and safety are lacking.

Therefore, we conducted this study to investigate the clinical effect of PCSK9 mAbs in patients with familial hypercholesterolemia to provide the basis for clinical practice.

Material and methods

Literature search

The published articles were searched by two researchers reporting on studies performed on the effect of PCSK9 mAbs in patients with FH. The search databases were Embase, PubMed, Web of Science, Google Scholar, and the Cochrane Library. Our search was limited to articles published up to 7 July 2021, using the following keywords related to PCSK9 inhibitors: "PCSK9 inhibitors" OR "alirocumab" OR "SAR236553" OR "monoclonal antibody REGN727" OR "REGN727 monoclonal antibody" OR "REGN727" OR "praluent" OR "SAR-236553" OR "REGN-727" OR "monoclonal antibody REGN727" OR "evolocumab" OR "repatha" OR "AMG145" in combination with words related to familial hypercholesterolaemia: "familial hypercholesterolemia" or "FH" or "hypercholesterolemia type II" or "Hyper-Low Density Lipoproteinemia" or "Hypercholesterolemic Xanthomatosis, Familial" or "Hyper beta Lipoproteinemia" or "LDL Receptor Disorder" or "Apolipoprotein B-100 Familial Defective" or "Hyperbetalipoproteinemia". The search was limited to humans and English language. Additionally, we examined the reference lists of the extracted articles. For studies with more than one report, we used the latest published report.

Inclusion and exclusion criteria

We selected studies examining the effect of PCSK9 inhibitors in patients with FH. The following inclusion criteria were used: (1) randomized controlled trials (RCTs) whose purpose was to evaluate the effect of PCSK9 mAbs in patients with FH; (2) the study subjects were patients with FH; (3) basic characteristics (e.g. age, sex, and race) were not statistically significant between two groups; (4) at least one of the observation groups was treated with PCSK mAbs; (5) PCSK mAbs had no limitations in usage and dose; and (6) sufficient data were provided in the referenced articles.

The following exclusion criteria were used: (1) nonclinical trials, case reports, or series; (2) animal trials; (3) retrospective, nonrandomized trials, and semirandomized controlled trials; (4) unable to extract data from the literature; articles with incomplete or incorrect data; and (5) no placebo control group was established.

Data extraction

Based on the latest search methods, two researchers reviewed the retrieved articles. The data extracted were as follows: first author's name, year of publication, country, sample size, average age, sex ratio, race, history of coronary artery disease, regimens, types of PCSK9 mAbs, follow-up, and endpoint. If the content of the article needed clarification, we attempted to discuss it with the authors of the article. If the data required for the analysis could not be retrieved, the article was excluded.

Risk-of-bias assessments

Two authors estimated the methodological quality of the included studies independently based on the Cochrane Risk of Bias criteria [13]. Five items were used to assess the bias in each trial: randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each quality item was graded as high risk, low risk, or some concerns.

Statistical analysis

Individual study results were summarized and analysed using Stata software version 12.0 (Stata Corp, College Station, TX). The risk ratio (RR) and 95% CI were used to statistically analyse the count data. The weighted mean difference (WMD) and 95% CI were used to analyse the continuous variables. When two-tailed P values were < 0.05, they were considered statistically significant. When the heterogeneity of the research was found to be substantial, we performed subgroup and sensitivity analyses to determine the sources of heterogeneity.

Results

Study selection and characteristics

Initially, 1488 articles were obtained by searching electronic databases, and the reference lists of relevant articles were retrieved. A total of 310 articles were filtered through title and abstract screening. Then, the full texts of the remaining articles were downloaded and evaluated in detail. Ultimately, a total of 2188 patients were included from 11 literature articles [14–23], including 1469 patients in the PCSK9 mAb group and 719 patients in the control group. The flow chart of the study selection process is shown in Figure 1. The basic characteristics of each included study are shown in Table 1.

Literature quality evaluation

The 11 articles were all RCTs [14–23], but not all the articles provided a description of the randomiza-

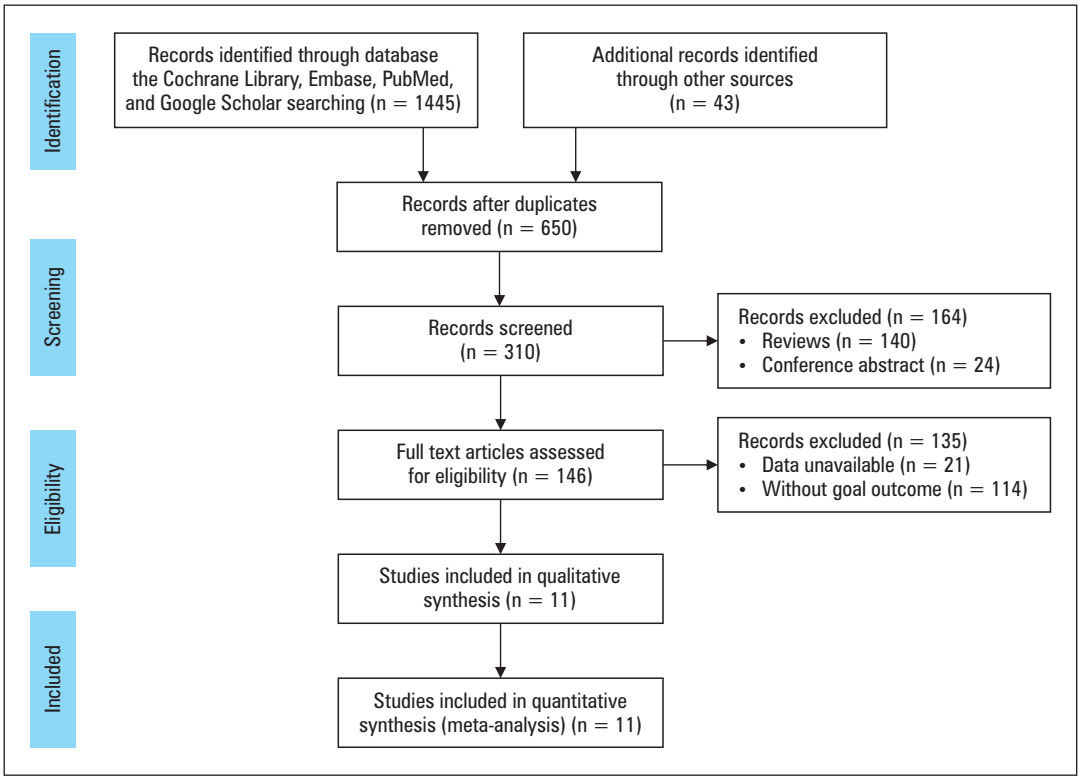

Figure 1. *Flowchart for the study selection*

tion method. All the studies provided the process of randomization and mentioned blinding of personnel and subjects. The literature quality score is shown in **Table 2.**

Efficacy endpoint

Percentage change of LDL-C

Ten studies (16 trial comparisons) [15–24] reported the percentage change in LDL-C in patients with FH. This meta-analysis showed that compared with placebo, PCSK9 mAb reduced the level of LDL-C in FH patients (WMD = –45.52, 95% CI: –49.70 to –41.34, I^2 = 99.6%), as shown in Figure 2. The random effect model was applied, and the heterogeneity was high. Thus, we performed the following subgroup analyses to explore the sources of heterogeneity.

Subgroup analysis

We analysed three subgroups according to the type of FH, the type of PCSK9 mAb, and the follow-up time. The subsequent subgroup analysis showed that compared to HoFH patients (WMD = –33.99, 95% CI: –38.15 to –29.82, I^2 = 46.2%), the change in LDL-C in patients with HeFH was more significant (WMD = –47.18, 95% CI: –51.49 to –42.86), as shown in Figure 3. In addition, compared with alirocumab (WMD = –43.68, 95% CI: –48.83 to –38.52), there was a more significant reduction in LDL-C with evolocumab (WMD = –48.56, 95% CI: –56.18 to –40.94), as shown in Figure 4. In addition, the results of the subgroup analysis according to the follow-up time are shown in Figure 5.

Safety endpoints

Treatment-emergent adverse events (TEAEs)

Ten studies (18 trial comparisons) [14–16, 18–24] reported TEAEs. TEAEs were defined as adverse events that developed, worsened, or became serious after the first injection and up to 10 weeks after the last injection. In total, 816 out of 1192 patients in the PCSK9 mAb group experienced TEAEs, while 390 out of 579 patients in the control group experienced TEAEs. The results showed that there was no significant difference between the experimental and control groups (RR = 1.03, 95% CI: 0.97 to 1.10, I^2 = 19.1%), as shown in Figure 6.

Serious adverse events (SAEs)

Nine studies (14 trial comparisons) [14, 16, 18–24] reported SAEs. SAEs were defined as adverse events that were fatal, life-threatening, required admission to hospital or prolonged stay in hospital, or caused persistent or significant disability or incapacity or a congenital anomaly or birth defect. In total, 83 out of 1130 patients in the PCSK9 mAb group experienced SAEs, while 41 out of 632 patients in the control group experienced SAEs. The results showed that there was no significant difference between the PSCK9 mAb group and control

Table 1. *Characteristics of studies included in the meta-analysis*

Author	Year	Country	Sample size		Average age, mean(SD)		Male, No. (%)		Race, White, n(%)		History of coronary artery disease		Regimens		Diagnosis	Types of PCSK9 inhibitor	Follow-up	Endpoints
			E	C	E	C	E	C	E	C	E	C	E	C				
Stein et al. a(1)	2012	Multicentre	5	6	NA	39.0	NA	5 (83)	NA	6 (100)	NA	NA	50 mg SC on days 1, 29, and 43	Placebo on days 1, 29, and 43	HeFH	Alirocumab	148 d	TEAE, SAE
Stein et al. b(1)	2012	Multicentre	5	6	NA	39.0	NA	5 (83)	NA	6 (100)	NA	NA	100 mg SC on days 1, 29, and 43	Placebo on days 1, 29, and 43	HeFH	Alirocumab	148 d	TEAE, SAE
Stein et al. c(1)	2012	Multicentre	5	6	NA	39.0	NA	5 (83)	NA	6 (100)	NA	NA	150 mg SC on days 1, 29, and 43	Placebo on days 1, 29, and 43	HeFH	Alirocumab	148 d	TEAE, SAE
Stein et al. a(2)	2012	USA and Canada	15	15	51.3 (7.7)	51.9 (9.6)	9 (60)	9 (60)	14 (93)	14 (93)	8	7	150 mg SC Q4W	Placebo Q4W	HeFH	Alirocumab	20 w	LDL-C, TEAE
Stein et al. b(2)	2012	USA and Canada	16	15	52.9 (11.2)	51.9 (9.6)	9 (56)	9 (60)	15 (94)	14 (93)	6	7	200 mg SC Q4W	Placebo Q4W	HeFH	Alirocumab	20 w	LDL-C, TEAE,
Stein et al. c(2)	2012	USA and Canada	15	15	54.3 (9.6)	51.9 (9.6)	7 (47)	9 (60)	15 (100)	14 (93)	7	7	300 mg SC Q4W	Placebo Q4W	HeFH	Alirocumab	20 w	LDL-C, TEAE
Stein et al. d(2)	2012	USA and Canada	16	15	56.3 (10.2)	51.9 (9.6)	13 (81)	9 (60)	15 (94)	14 (93)	4	7	150 mg SC Q2W	Placebo Q2W	HeFH	Alirocumab	20 w	LDL-C, TEAE
Kastelein et al. a	2015	North America, Europe, and South Africa	323	163	52.1 (12.9)	51.7 (12.3)	180 (55.7)	94 (57.7)	300 (92.9)	144 (88.3)	147	78	75/150 mg SC Q2W	Placebo Q2W	HeFH	Alirocumab	78 w	LDL-C, TEAE, SAE
Kastelein et al. b	2015	Europe	167	82	53.2 (12.9)	53.2 (12.5)	86 (51.5)	45 (54.9)	164 (98.2)	80 (97.6)	58	31	75/150 mg SC Q2W	Placebo Q2W	HeFH	Alirocumab	78 w	LDL-C, TEAE, SAE
Robinson et al.	2015	Africa, Europe, and North and South America	276	139	NA	NA	NA	NA	NA	NA	NA	NA	150 mg SC Q2W	Placebo Q2W	HoFH	Alirocumab	78 w	LDL-C
Ginsberg et al.	2016	Canada, the United States, the Netherlands, Russia, and South Africa	72	35	49.8 (14.2)	52.1 (11.2)	35 (48.6)	22 (62.9)	64 (88.9)	30 (85.7)	31	22	150 mg SC Q2W	Placebo Q2W	HeFH	Alirocumab	78w	LDL-C, TEAE, SAE
Moriarty et al.	2016	USA and Germany	41	21	59.5 (9.2)	57.0 (10.5)	26 (63.4)	10 (47.6)	39 (95.1)	21 (100)	35	14	150 mg SC Q2W	Placebo Q2W	HeFH	Alirocumab	18 w	LDL-C, TEAE, SAE

Table 1. *Characteristics of studies included in the meta-analysis*

Author	Year	Country	Sample size		Average age, mean(SD)		Male, No. (%)		Race, White, n(%)		History of coronary artery disease		Regimens		Diagnosis	Types of PCSK9 inhibitor	Follow-up	Endpoints
			E	C	E	C	E	C	E	C	E	C	E	C				
Blom et al.	2020	Multicentre	45	24	42.3 (14.1)	45.4 (15.8)	21 (46.7)	13 (54.2)	36 (80.0)	18 (75.0)	21	9	150 mg SC Q2W	Placebo Q2W	HeFH	Alirocumab	32 w	LDL-C, TEAE, SAE
Raal et al. a	2012	North America, Western Europe, Hong Kong, Singapore, and South Africa	55	56	47.6 (13.6)	49.3 (11.3)	30 (54.5)	24 (42.9)	48 (87.3)	48 (85.7)	11	10	350mg SC Q4W	Placebo Q4W	HeFH	Evolocumab	12w	LDL-C, TEAE, SAE
Raal et al. b	2012	North America, Western Europe, Hong Kong, Singapore, and South Africa	56	56	51.8 (13.0)	49.3 (11.3)	35 (62.5)	24 (42.9)	52 (92.9)	48 (85.7)	14	10	420mg SC Q4W	Placebo Q4W	HoFH	Evolocumab	12w	LDL-C, TEAE, SAE
Raal et al. a	2015	Australia, Asia, Europe, New Zealand, North America, and South Africa	110	54	52.6 (12.3)	51.1 (14.2)	66 (60)	29 (54)	NA	NA	38	16	140 mg SC Q2W	Placebo Q2W	HeFH	Evolocumab	12w	LDL-C, TEAE, SAE
Raal et al. b	2015	Australia, Asia, Europe, New Zealand, North America, and South Africa	110	55	51.9 (12.0)	46.8 (12.1)	64 (58)	31 (56)	NA	NA	39	10	420 mg SC Q4W	Placebo Q4W	HeFH	evolocumab	12w	LDL-C, TEAE, SAE
Raal et al.	2015	North America, Europe, the Middle East, and South Africa	33	16	30.0 (12.0)	32.0 (14.0)	17 (48)	8 (50)	29 (88)	15 (94)	15	6	420 mg SC Q4W	Placebo Q4W	HeFH	evolocumab	12w	LDL-C, TEAE, SAE
Santos et al.	2020	North America, Latin America, Europe, and the Asia–Pacific region	104	53	13.7 (2.3)	13.7 (2.5)	43 (41)	26 (49)	89 (86)	44 (83)	NA	NA	420 mg SC Q4W	Placebo Q4W	HeFH	evolocumab	24w	LDL-C, TEAE, SAE

PCSK9 — proprotein convertase subtilisin/kexin type 9, FH — familial hypercholesterolaemia, SC — subcutaneous, HeFH — heterozygous familial hypercholesterolaemia, HoFH — homozygous familial hypercholesterolaemia, LDL-C — low-density lipoprotein cholesterol, SAE — serious adverse event, TEAE — treatment-emergent adverse event

Table 2. *Assessment of methodological quality of included studies*

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Stein et al.	Low	Low	Low	Low	Low	Low
Stein et al.	Low	Low	Low	Low	Low	Low
Kastelein et al.	Low	Low	Low	Low	Low	Low
Robinson et al.	Low	Low	Low	Low	Low	Low
Ginsberg et al.	Low	Low	Low	Low	Low	Low
Moriarty et al.	Low	Low	Low	Low	Low	Low
Blom et al.	Low	Low	Low	Low	Low	Low
Raal et al.	Low	Low	Low	Low	Low	Low
Raal et al.	Low	Low	Low	Low	Low	Low
Raal et al.	Low	Low	Low	Low	Low	Low
Santos et al.	Low	Low	Low	Low	Low	Low

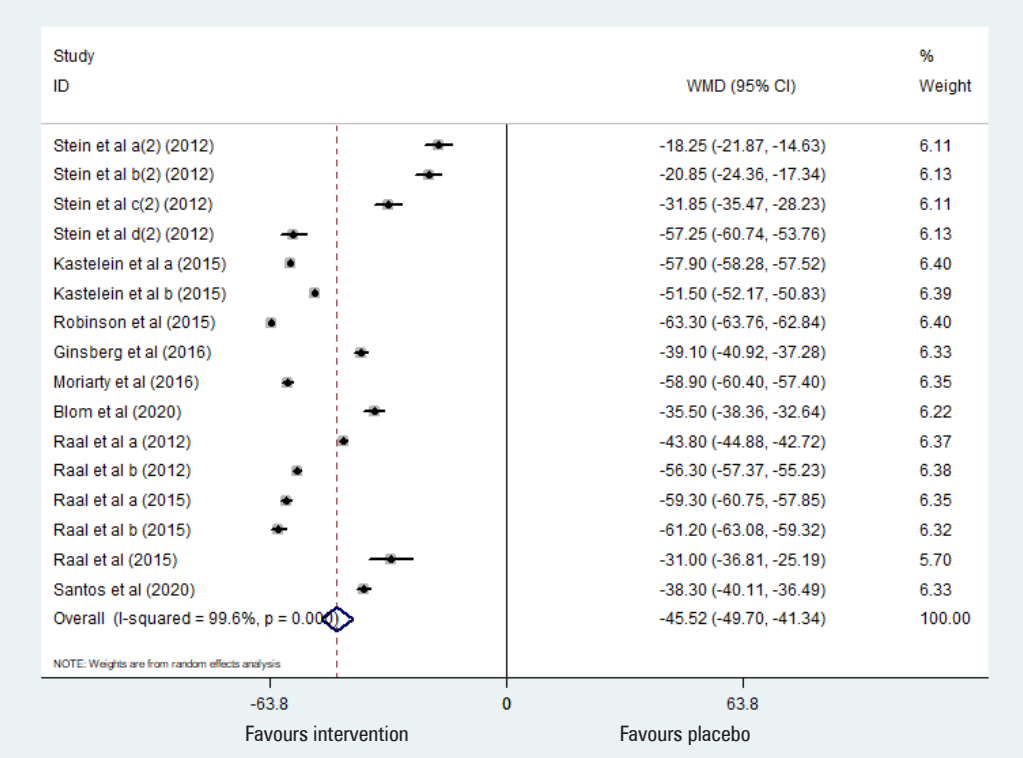

Figure 2. *Comparison of the percentage change in low-density lipoprotein cholesterol (LDL-C) between the experimental and control groups. WMD — weighted mean difference*

group (RR = 1.02, 95% CI: 0.72 to 1.44, I^2 = 0.0%), as shown in Figure 7.

Publication bias and sensitivity analysis

Begg's test and Egger's test showed that there was a high probability of publication bias in changes in LDL-C among the retrieved articles, as shown in Supplementary File — Figures S1–2. Begg's test and Egger's test also showed that there was a low probability of publication bias in TEAEs among the retrieved articles, as shown in Supplementary File — Figures S3–4. The results of the sensitivity analysis on changes in LDL-C are shown in Supplementary File — Figure S5.

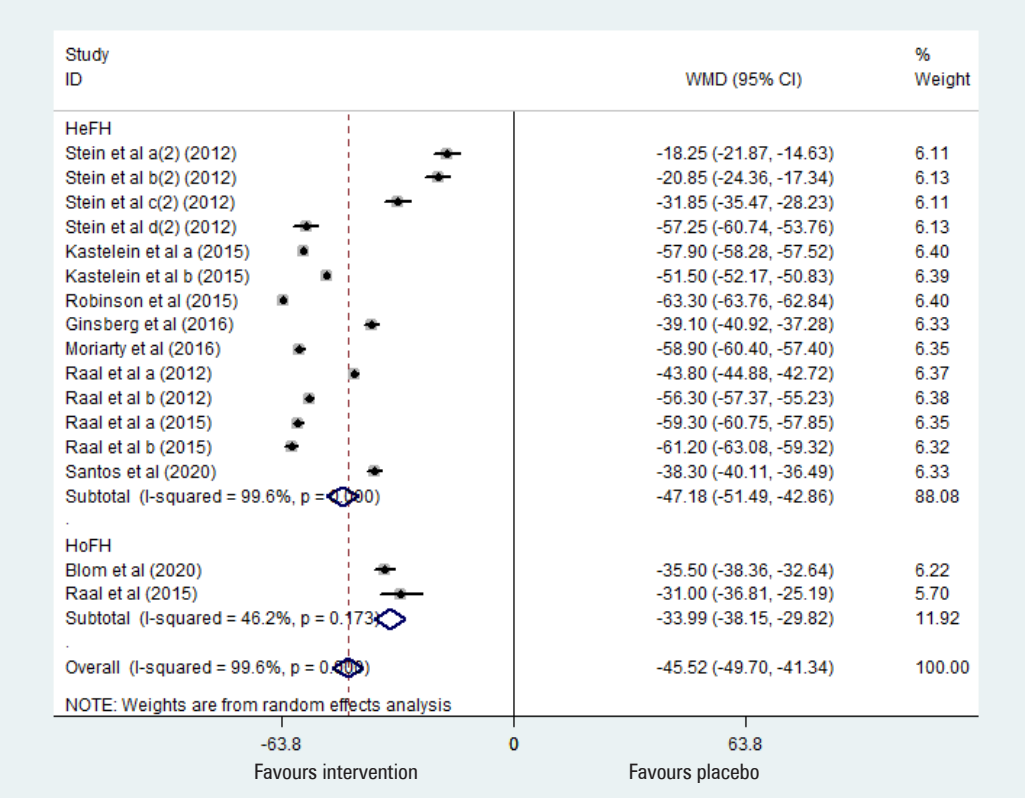

Figure 3. *Comparison of the percentage change of low-density lipoprotein cholesterol (LDL-C) between the experimental and control groups (subgroup analysis according to types of FH). WMD — weighted mean difference*

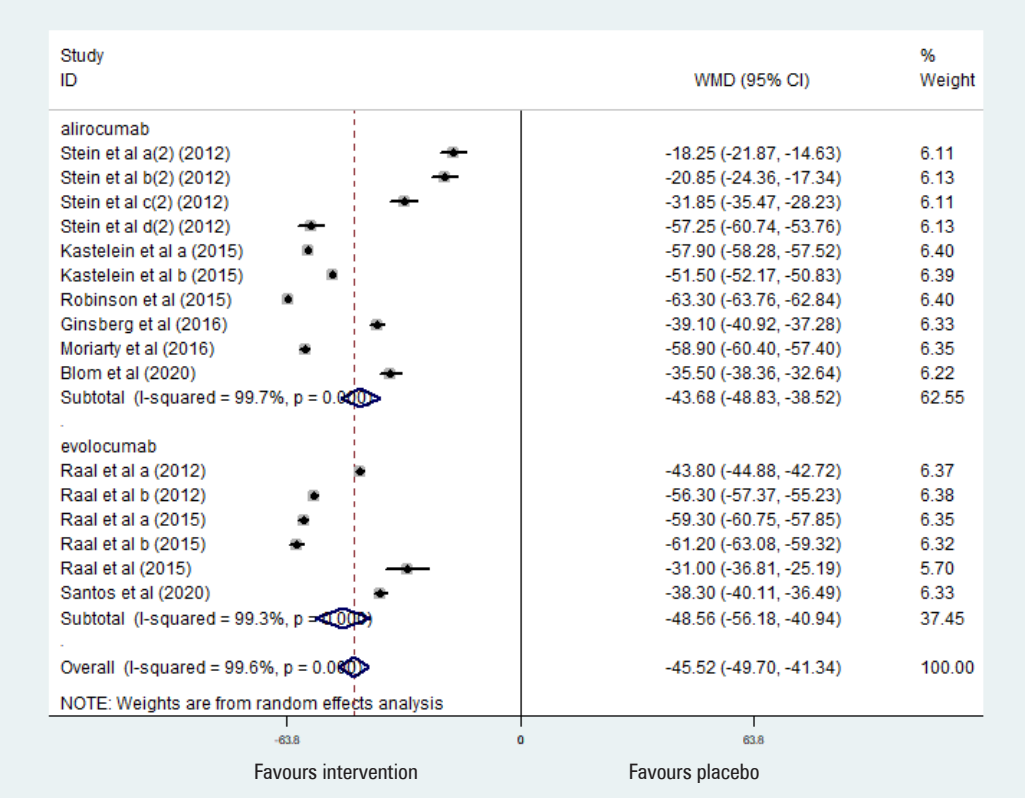

Figure 4. *Comparison of the percentage change of low-density lipoprotein cholesterol (LDL-C) between the experimental and control groups (subgroup analysis according to types of PCSK9 mAb). WMD — weighted mean difference; CI — confidence interval*

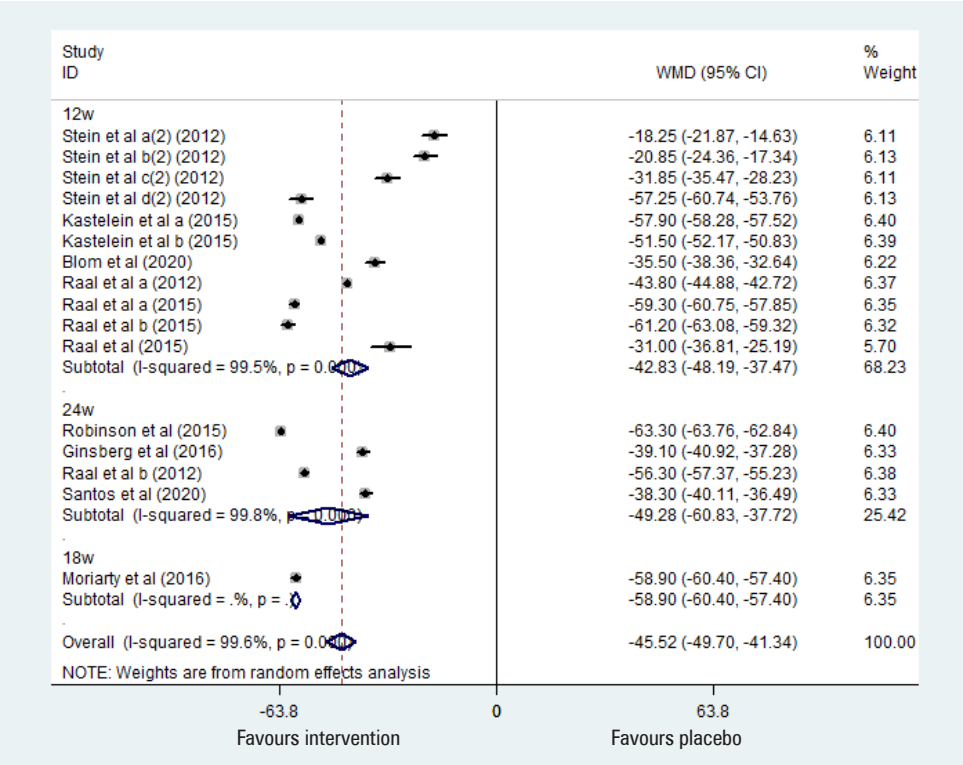

Figure 5. *Comparison of the percentage change of low-density lipoprotein cholesterol (LDL-C) between the experimental and control groups (subgroup analysis according to follow-up time). WMD — weighted mean difference; CI — confidence interval*

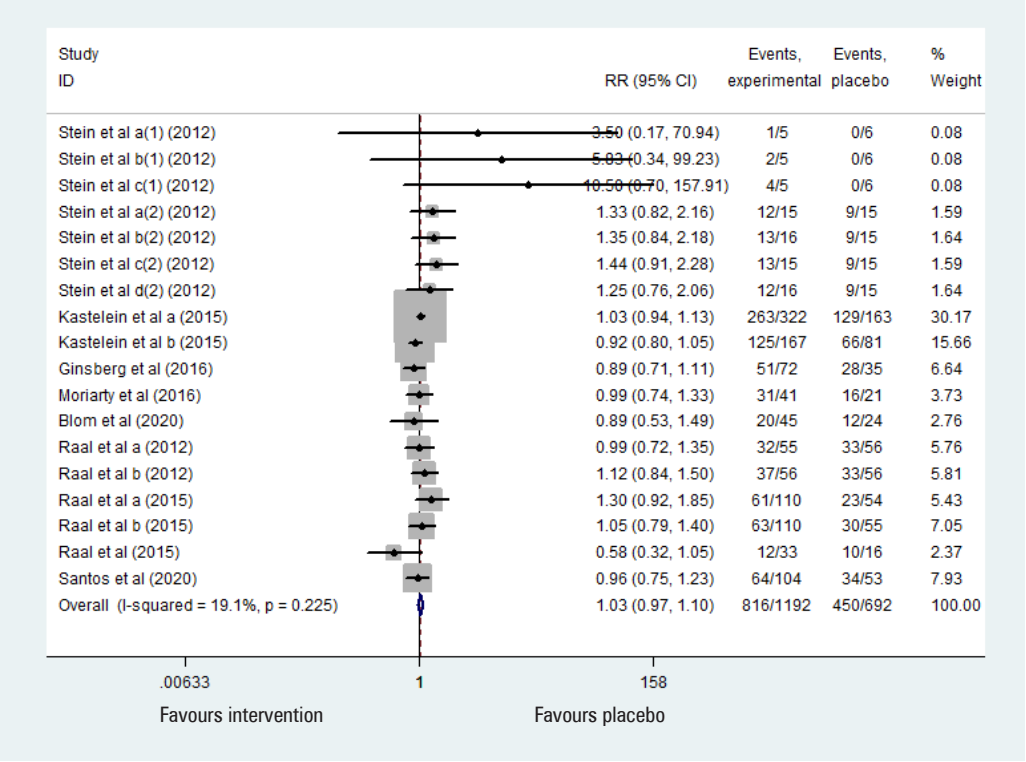

Figure 6. *Comparison of treatment-emergent adverse events (TEAEs) between the experimental and control groups. RR — rate ratio; CI — confidence interval*

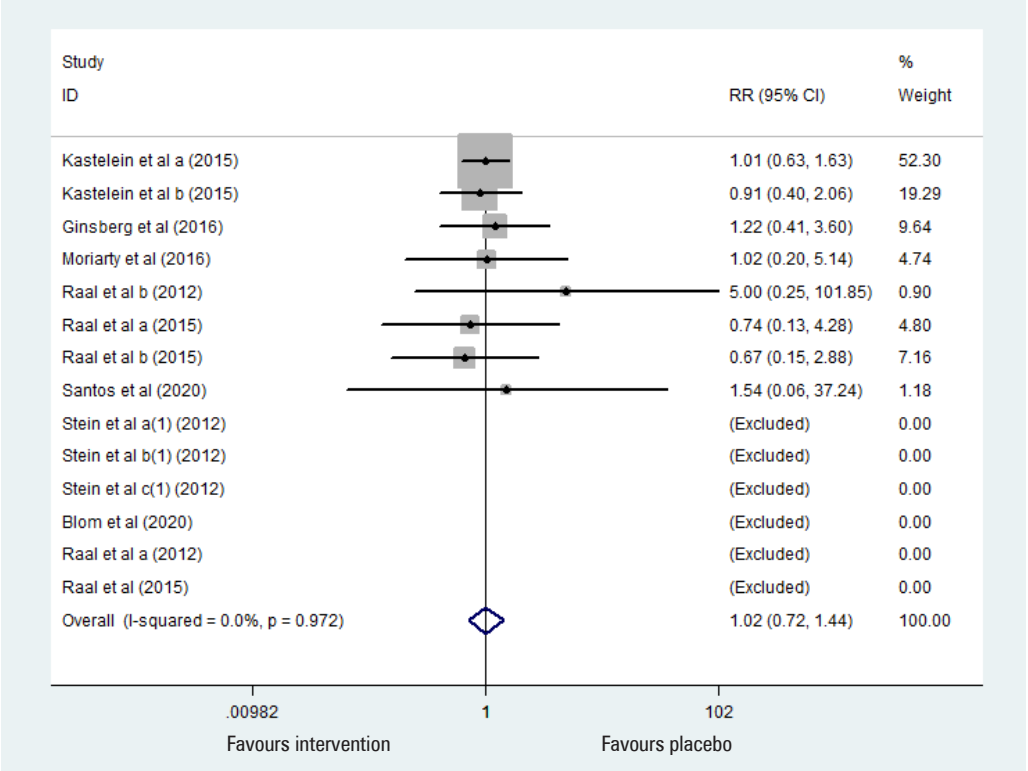

Figure 7. *Comparison of serious adverse events (SAEs) between the experimental and control groups. RR — rate ratio; CI — confidence interval*

Discussion

FH is a disorder of abnormal LDL metabolism that leads to the early development of atherosclerosis cardiovascular disease (ASCVD) in humans [25]. This is strong evidence for the cholesterol theory in the pathogenesis of ASCVD. The FH aetiology of autosomal dominant inheritance is caused by one or more of the following three gene mutations: LDLR, ApoB, and PCSK9 [26, 27]. The observation of a large number of clinical cases shows that the common features of the phenotype of patients with FH are significantly elevated LDL-C levels, extensive yellow tumours, and early-onset, multisite, rapidly progressive ASCVD [28].

PCSK9 mAbs can block the degradation of LDL-R in hepatocytes and increase the expression of LDL-R on the surface of hepatocytes, thus promoting LDL-C metabolism and reducing serum LDL-C concentration [29]. PCSK9 mAbs have potent cholesterol-lowering effects, significantly reducing LDL-C levels. The main PCSK9 monoclonal antibodies currently used in the clinic are alirocumab and evolocumab [30].

In recent years, the study of PCSK9 mAbs in patients with familial hypercholesterolaemia has attracted a lot of attention. A meta-analysis by Qian et al. [31] including 15 RCTs indicated that PCSK9-mAb contributes to decreased levels of LDL-C and other lipids in familial hypercholesterolaemia and statin-intolerant patients with satisfactory safety and tolerability. Both familial and nonfamilial hypercholesterolaemic patients were included in his study. A meta-analysis by Eslami et al. [32] indicated that evolocumab, as a PCSK9 mAb, could ameliorate the lipid profile in FH patients. Evolocumab decreased the levels of not only LDL-C but also other lipoprotein markers and significantly increased HDL-C levels. However, the efficacy of alirocumab was not mentioned in the study. Li et al. [33] revealed that in patients with FH, PCSK9 antibody therapy satisfactorily regulated lipid levels, especially reducing serum levels of LDL-C. PCSK mAbs have good safety and a good tolerance profile with short-term administration for FH. Despite these findings, the patient sample sizes were small in these articles. Whether PCSK9 mAbs are safe and effective in FH patients remains controversial. Because a few new RCTs were published in 2017–2021, it is necessary to perform an analysis to re-assess the efficacy and safety of PCSK mAbs in patients with FH.

In our study, 2188 patients were allocated either to the PCSK9 mAb group (n = 1469) and the control group (n = 719). This meta-analysis indicated that PCSK9 mAb reduced the percentage change of LDL-C in FH patients compared with placebo (WMD = –45.52, 95% CI: –49.70 to –41.34, I^2 = 99.6%). The heterogeneity was high; thus, we analysed three subgroups according to the type of

FH, type of PCSK9 mAb, and follow-up time to better explore sources of heterogeneity. However, a large amount of heterogeneity still existed after subgroup analysis. We performed sensitivity analysis but did not find a source of heterogeneity. We considered that this may be caused by different doses of PCSK9 mAbs. In addition, there was no significant difference between the two groups in the incidence of TEAEs (RR = 1.03, 95% CI: 0.97 to 1.10, I^2 = 19.1%) and SAEs (RR = 1.02, 95% CI: 0.72 to 1.44, I^2 = 0.0%).

This meta-analysis has the following advantages: (1) The 11 articles included in this study were all multicentre RCTs. (2) Our analysis included 11 studies and had a larger sample size covering the types of HF, follow-up time, and types of PCSK mAbs in detail, which increases the credibility of our research. (3) We found that PCSK mAbs may increase the incidence of SAE, which was not reported in previous studies. (4) The sample we included in the study included both children and adults.

The limitations of our meta-analysis include the following: (1) There was a high probability of publication bias on changes in LDL-C among the included articles. (2) There was no uniformity in the PCSK9 mAb doses and time of application, which will introduce deviations among study outcomes. (3) The heterogeneity was high regarding the percentage change of LDL-C. (4) Almost 80% of the individuals in the samples were white, so the use of PCSK9 mAbs in other ethnic groups needs to be studied. (5) Short- and long-term indicators were lacking to evaluate the preventive effects of PCSK9 mAbs in patients with FH. Short-term changes in LDL-C cannot represent long-term outcomes and therefore require extended follow-up to determine the patient's outcome. However, due to the limitations of quantity, quality, and data from the articles, further large-scale and even global studies are required.

Hence, our updated meta-analysis suggests that evolocumab is more effective in decreasing the level of LDL-C in patients with HeFH. Our research also hints that future RCTs should concentrate on the following aspects: (1) Due to national and ethnic differences, multiracial RCTs are needed to assess the efficacy of PCSK9 mAbs. (2) The long-term indicators to assess the clinical effect of PCSK9 mAb should be increased to improve the reliability of the results.

Conclusions

In summary, our meta-analysis demonstrated that PCSK9 mAbs reduce the percentage change in LDL-C. In addition, there was no significant difference between the experimental and placebo groups in the incidence of TEAEs and SAEs. In the future, as research continues, large-scale, high-quality RCTs will emerge. Meta-analyses based on these RCTs will provide more accurate results that will provide a basis for improving the clinical management of FH.

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