Systematic Review

Effects of alirocumab on cardiovascular events and all-cause mortality: a systematic review and meta-analysis

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Evaluation of the effects of alirocumab on cardiovascular (CV) events, CV mortality and all-cause mortality. Data search was carried out using the Cochrane Library, PubMed, Web of Science and Embase. The search time is up to November 18, 2020. All randomized clinical trials (AEs) comparing alirocumab with placebo were searched. Meta-analysis was performed by Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and the heterogeneity between studies was tested by Cochrane's Q test and measured with I2 statistics. A total of 13 randomized controlled trials with 24,815 participants were included. Alirocumab usage can considerably lower the incidence of CV events when compared to the control group (risk ratio(RR) 0.89, 95% confidence interval(CI) 0.83–0.95). No significant difference in CV mortality between the two groups was observed (RR 0.87, 95% CI 0.74–1.04). Treatment with alirocumab has been associated with a major decrease in all-cause mortality compared to placebo (RR 0.80, 95% CI 0.66–0.96). The incidence of serious adverse events (AEs) was similar in the two groups (RR 0.94, 95% CI 0.90–0.99). Alirocumab can reduce CV events and all-cause mortality. The AEs were mild and tolerable.

Keywords

Alirocumab; CV events; All-cause mortality; Meta-analysis

1. Introduction

Both in Western countries and some Eastern countries, cardiovascular (CV) disease has been the main cause of death in recent years [1, 2]. The level of LDL cholesterol (LDL-C) in plasma is one of the main risk factors for CV [3]. The decrease in LDL-C levels has been reported to be associated with a linear decrease in the risk of CV [4, 5].

Proprotein convertase subtilisin/kexin type 9 (PCSK-9) is a serine protease that promotes the degradation of LDL receptors and decreases the ability of the liver to remove LDL-C from circulation [6, 7]. Alirocumab is a human monoclonal antibody that inhibits human PCSK-9. Alirocumab inhibits hepatic LDLR degradation, increases liver clearance of LDL-C, and reduces plasma LDL-C concentration by binding to circulating PCSK9 [8]. Randomized controlled trial (RCT) data from ODYSSEY results indicate that alirocumab has significant clinical benefits in subjects at high CV risk [9]. However, alirocumab did not reduce the incidence of CV events compared with ezetimibe in the ODYSSEY COMBO II trial. Although meta-analysis has evaluated the effect of PCSK-9 inhibitors on incidence of CV disease and all-cause mortality [10, 11], there is no systematic meta-analysis to directly assess the impact of alirocumab on CV events. Therefore, the evidence for such drugs should be evaluated and synthesized in a timely manner. The purpose of this study is to systematically review and compile all available Alirocumab RCTs in order to assess their effect on CV events, CV mortality, all-cause mortality and adverse events (AEs).

2. Methods

This study was performed in accordance with the PRISMA (Preferred Reporting of Systematic Reviews and Meta-Analysis) (**Supplementary Table 1**).

2.1 Literature searches and study selection

The PubMed, Cochrane Library, Web of Science and Embase databases were searched until November 18, 2020. The search terms were searched using keywords and Mesh terms, as shown below: alirocumab, SAR236553, REGN-727, randomized controlled trials and clinical trials, etc. We also searched manually for references to included studies and current systematic reviews to identify any other publications that could be potentially relevant. The search is limited to English.

The inclusion criteria were as follows: (1) RCTs published in peer-reviewed journals; (2) Comparison of Alirocumab and control (placebo or alternative lipid-lowering therapy); (3) Report data on CV events, CV mortality, all-cause mortality or AEs.

The Reviews, reports, non-randomized studies, and studies using other anti-PCSK9 antibodies (e.g., evolocumab, bococizumab) were excluded.

2.2 Data extraction and quality assessment

Two investigators used the prespecified data collection form to extract data independently. The following data were mainly extracted: first author, publication year, number of participants and average age range, treatment, participant characteristics, intervention type, median follow-up time, and relevant data on outcome indicators. The third author

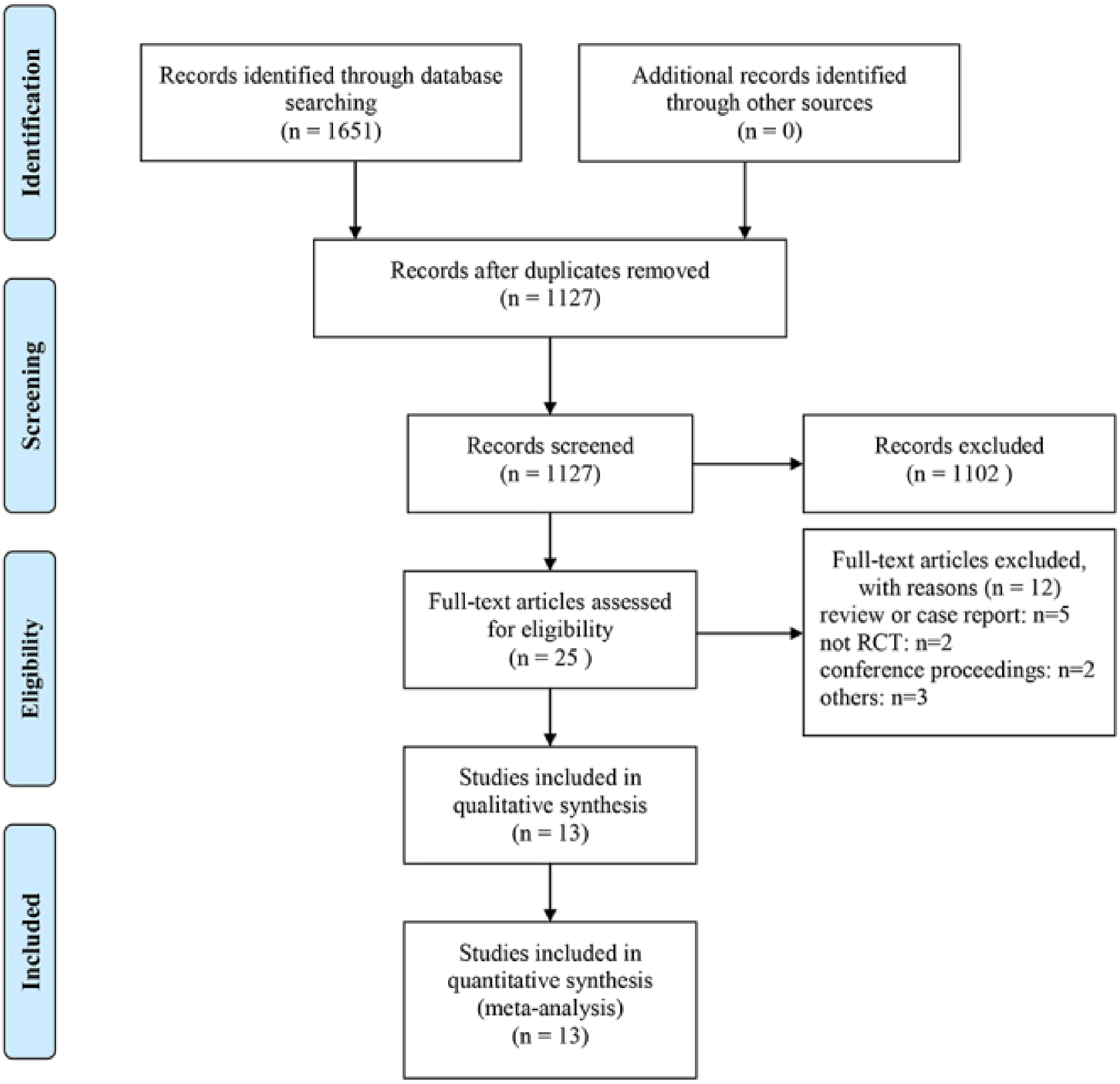

Fig. 1. Flow diagram showing the study selection process for the meta-analysis. The number of studies shown at the bottom of the flow chart represents studies that were ultimately considered eligible for inclusion in this meta-analysis.

cross-checked all entries and arbitrated for any inconsistencies. Besides, the risk of bias in the included trials was evaluated using the Cochrane Collaboration's method.

2.3 Statistical analysis

Meta-analysis was conducted using Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). The risk ratio (RR) was used for dichotomous variables, and the variables were expressed in 95% confidence intervals (CI). The heterogeneity of each outcome in the trial was estimated by χ^2 test and quantified by I^2 statistics. If $I^2 \leq 50\%$, the heterogeneity was considered low and the data was analyzed using a fixed model. If $I^2 > 50\%$, the heterogeneity was considered high, a random model was used to analyze the data, and a subgroup analysis or sensitivity analysis was used to resolve heterogeneity. The publication bias was checked by the funnel plot.

3. Results

3.1 Baseline characteristics

Fig. 1 shows the document screening flow chart of this study. A total of 1651 articles were obtained in the initial literature search. After the screening of the titles and abstracts, 25 studies met the criteria for a full-text review. Following the screening of the titles and abstracts, 25 papers were qualified for a full text analysis and 13 of them were included in the final review [9, 12–23]. Thirteen studies included 24,815 patients, of which 13,245 were allocated to the alirocumab intervention and 11,570 were allocated to the control group. In the included trials, patients took 75 mg of alirocumab every 2 weeks and then increased to 150 mg every 2 weeks partway throughout the trial based on the LDL-C response. The duration of the intervention ranged between 24 weeks and 146 weeks. The average age was between 51.7 and 64.6 years, and

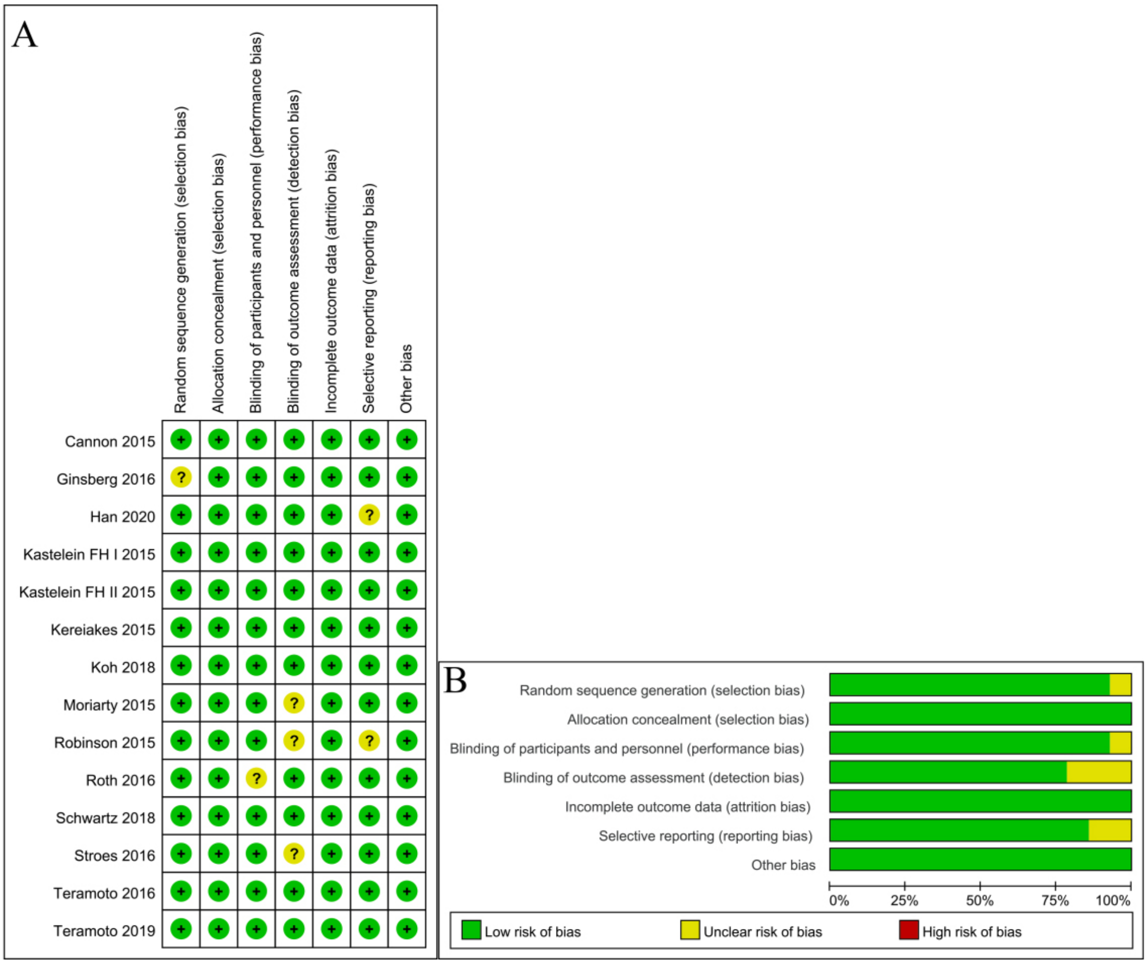

Fig. 2. Risk of bias assessment in randomized controlled trials (RCTs). (A) The risk of bias summary of the included RCTs. Green represents low risk, yellow unclear risk, and red high risk. (B) The risk of bias graph of the included RCTs. Green represents low risk, yellow unclear risk, and red high risk.

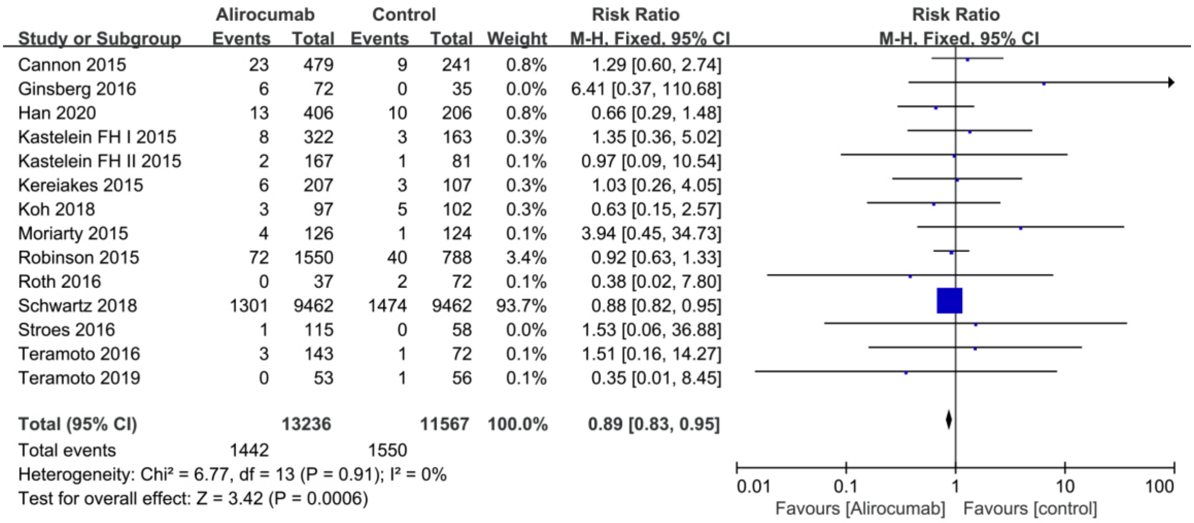

Fig. 3. Association of alirocumab compared with placebo with the incidence of CV events. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names.

Fig. 4. Association of alirocumab compared with placebo with the incidence of CV mortality. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names.

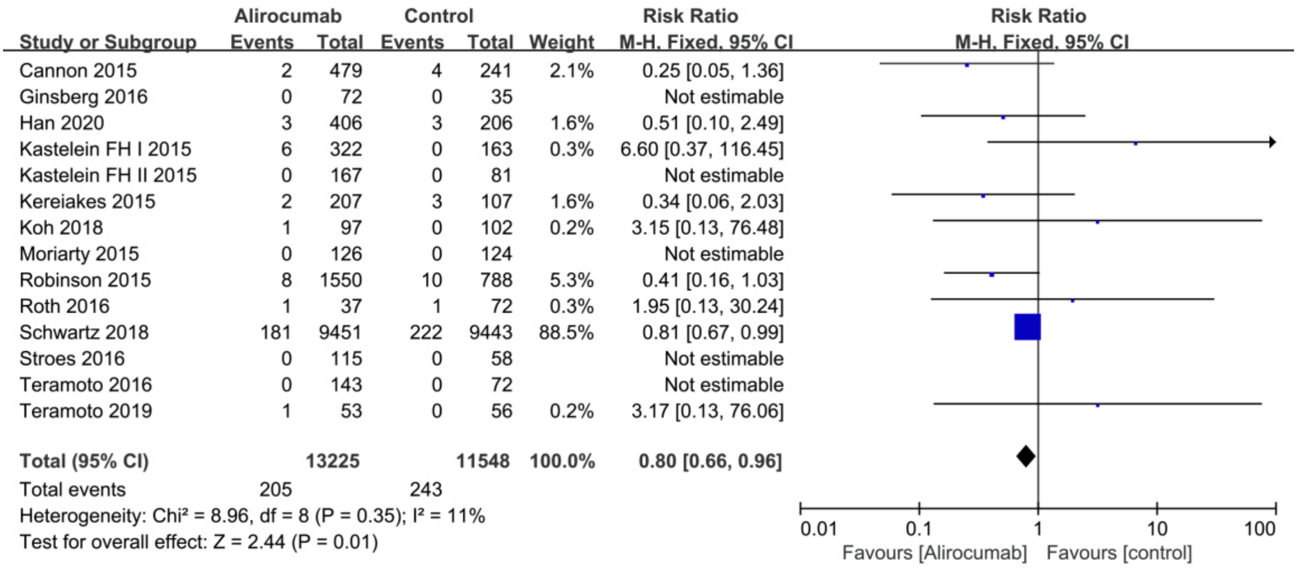

Fig. 5. Association of alirocumab compared with placebo with the incidence of all-cause mortality. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names.

72.3% of the patients are male. Baseline patient characteristics for the study arms included were shown in Table 1 (Ref. [9, 12–23]). The overall quality of included studies was moderate, and the risk of bias for most items was low (Fig. 2).

3.2 CV events

The CV events analysis included 13 RCTs (including 24,803 patients). Alirocumab treatment can dramatically lower the incidence of CV events when compared to the control group (10.9% versus 13.4%; RR 0.89, 95% CI 0.83–0.95; I^2 = 0%; P = 0.0006) (Fig. 3).

3.3 CV Mortality

The incidence of CV mortality was reported in four RCTs (including 20,570 patients). There was no significant difference in CV mortality between alirocumab and the control groups (2.3% versus 2.7%; RR 0.87, 95% CI 0.74–1.04; I^2 = 0%; P = 0.12) (Fig. 4).

3.4 All-cause mortality

A total of 13 studies (including 24,773 patients) were included in the analysis of all-cause mortality. Compared with placebo, alirocumab can reduce the all-cause mortality of patients (1.6% versus 2.1%; RR 0.80, 95% CI 0.66–0.96; I^2 = 11%; P = 0.01) (Fig. 5).

3.5 AEs

Thirteen studies were included in the analysis of SAEs, including 24,748 patients. A substantial 2.2% decrease in the occurrence of severe AEs (SAEs) was observed in the alirocumab group relative to the control group (RR 0.94, 95% CI 0.90–0.99; I^2 = 0%; P = 0.01) (Fig. 6A). However, there was no significant difference in the risk of AEs between the alirocumab group and the control group. (RR 0.99, 95% CI 0.97–1.00; I^2 = 0%; P = 0.01) (Fig. 6B).

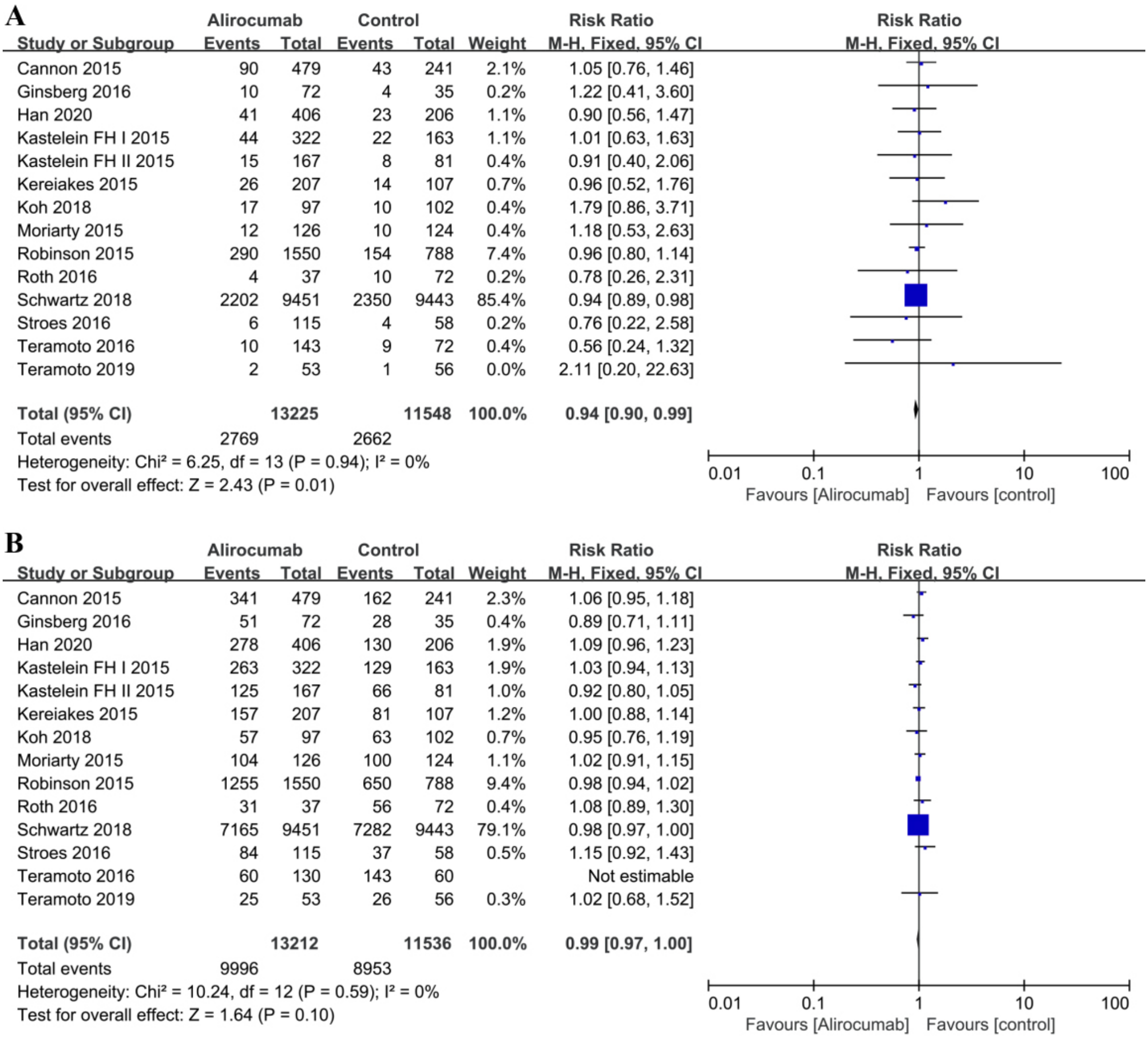

Fig. 6. Forest plots showing the effect of clinical outcomes on the SAEs and AEs. (A) Association of alirocumab compared with placebo with the incidence of SAEs. (B) Association of alirocumab compared with placebo with the incidence of AEs. Each square shows effect estimate of individual studies with their 95% CI. Size of squares is proportional to the weight of each study in the meta-analysis. In this plot, studies are shown in the order of publication date and first author's names.

3.6 Publication bias and sensitivity analyses

Funnel plot symmetry evaluation did not show any signs of publication bias for CV events, all-cause mortality or safety (Fig. 7). The sensitivity analysis omitted one study at a time and did not yield different results in terms of CV events, CV mortality, all-cause mortality, and AEs (**Supplementary Fig. 1**).

4. Discussion

Alirocumab is a human monoclonal antibody against PCSK-9. It is administered by subcutaneous injection every 2 weeks. The initial dose is 75 mg, the dose can be increased to 150 mg if LDL-C is not sufficiently reduced. In this study, a meta-analysis of RCTs was undertaken to examine the effect of treatment with alirocumab vs. placebo on CV events, CV mortality, all-cause mortality and SAEs. However, no difference was observed in CV mortality. The results of this meta-analysis are basically consistent with the results of the previous meta-analysis that evaluated PCSK-9 inhibitor [10, 11].

In the ODYSSEY experiment, no difference was reported in CV mortality or all-cause death or SAEs, except that the composite primary endpoint was significantly reduced [9]. The study found that patients who received alirocumab had a lower risk of CV events compared with patients who received placebo. Moreover, alirocumab can significantly reduce the risk of CV events in patients with baseline LDL cholesterol

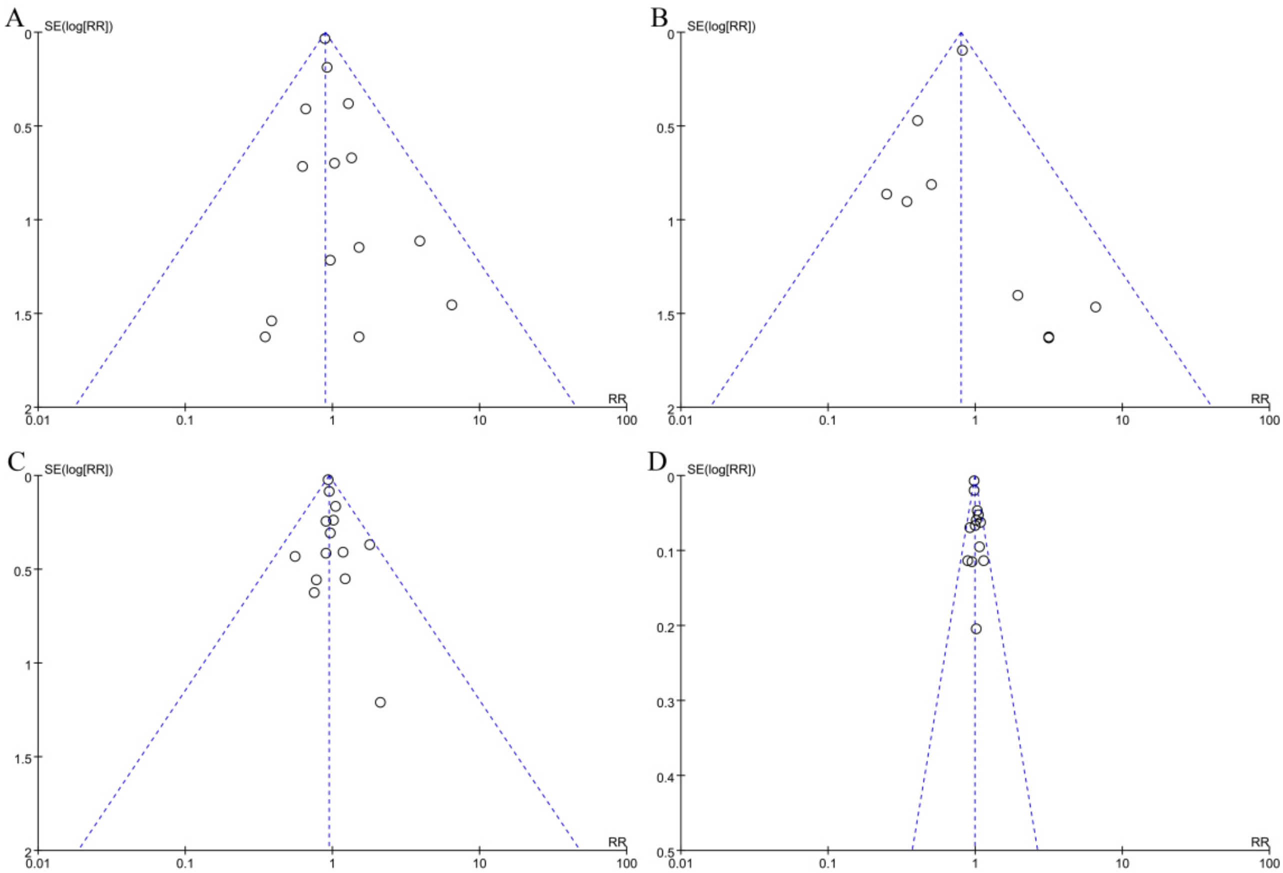

Fig. 7. Funnel plot of CV events. (A), all-cause mortality (B), SAEs (C) and AEs (D). Funnel plot of MACE depicting the publication bias of CV events, all-cause mortality, SAEs and AEs between alirocumab and placebo groups. Funnel plot is symmetrical distribution, which represents a low publication bias.

$\geq$100 mg/dL compared to patients with low baseline LDL cholesterol levels [24]. Although it is not statistically significant in terms of CV mortality, there is also a decreasing trend. It can be seen that alirocumab has benefits for CV events, and patients with higher baseline LDL-C levels may benefit more from CV events than patients with lower baseline LDL-C levels.

However, it has been reported that a delay between the effect on LDL-C levels and the appearance of clinical benefit has been observed in clinical trials of statins [10]. Furthermore, it was also observed that the extent of the risk mitigation of the secondary tended to increase over time in the FOURIER and ODYSSEY OUTCOMES studies [9, 25]. These results indicate that it takes time to convert LDL-C reduction into CV benefits, and the longer the follow-up time, the more obvious the benefits of CV events observed.

Although there is no significant difference in CV mortality between the alirocumab and control groups, alirocumab can significantly lower all-cause mortality, which may be connected to the risk of non-CV mortality. It is reported that alirocumab reduces non-fatal cardiovascular events and may have an impact on non-cardiovascular and cardiovascular deaths, which in turn affects all-cause deaths [26]. Despite this, current research is divided on whether alirocumab will lower all-cause mortality [10, 27, 28]. Previous research has revealed that statin medication required 5 to 6 years of exposure to observe the advantages of cholesterol-lowering treatment on mortality [29]. Therefore, additional and longer follow-up trials may be required to determine the advantages of alirocumab on all-cause mortality.

Regarding safety, this study showed that alirocumab had mild AEs and all-cause mortality was significantly lower than placebo. The incidence of SAEs was similar between alirocumab and placebo group. There was no statistically significant difference in the incidence of AEs between alirocumab and placebo.

This study presents an analysis on a topic on which numerous papers have already been published. The study analyzed CV events and CV mortality, and included all clinical trials published thus far. However, this study has some limitations. First of all, the follow-up time of the included studies is too short. Most studies have a follow-up time of 12 or 24 weeks. The long-term effect is not apparent. Secondly, ODYSSEY OUTCOMES contributed more than 85% of the data for all results and strongly influenced all effect estimates.

Table 1. Baseline characteristics of included studies.

Study	Intervention	N	Male	Age, y mean (SD) or median (range)	Body mass index (kg/m^2)	Patients	Background treatment	Follow-up duration, weeks
Cannon 2015 [12]	Alirocumab 75/150 Q2W	479	360	61.7 ± 9.4	30.0 ± 5.4	hypercholesterolaemia and established CHD or CHD risk-equivalents	a maximally tolerated dose of statin	104
	Ezetimibe	241	170	61.3 ± 9.2	30.3 ± 5.1			
Kastelein FH I 2015 [15]	Alirocumab 75/150 Q2W	323	180	52.1 ± 12.9	29.0 ± 4.6	HeFH	stable high dose statin	88
	Placebo	163	94	51.7 ± 12.3	30.0 ± 5.4			
Kastelein FH II 2015 [15]	Alirocumab 75/150 Q2W	167	86	53.2 ± 12.9	28.6 ± 4.6	HeFH	stable high dose statin	88
	Placebo	82	45	53.2 ± 12.5	27.7 ± 4.7			
Kereiakes 2015 [16]	Alirocumab 75/150 Q2W	209	131	63.0 ± 9.5	32.62 ± 6.30	high CV risk	a stable, maximally tolerated statin dose	24
	Placebo	107	77	63.0 ± 8.8	32.03 ± 7.07			
Moriarty 2015 [18]	Alirocumab 75/150 Q2W	126	70	64.1 ± 9.0	29.6 ± 6.6	moderate or high CV risk	no statin/stable dose of statin	24
	Ezetimibe	125	67	62.8 ± 10.1	28.4 ± 4.9			
Robinson 2015 [19]	Alirocumab 75/150 Q2W	1553	983	60.4 ± 10.4	30.2 ± 5.7	LDL-C ≥70 mg/dL	a maximally tolerated dose of statin	78
	Placebo	788	474	60.6 ± 10.4	30.5 ± 5.5			
Ginsberg 2016 [13]	Alirocumab 75/150 Q2W	72	35	49.8 ± 14.2	28.8 ± 5.2	HeFH and LDL-C ≥160 mg/dL	a maximally tolerated stable dose of statin	88
	Placebo	35	22	52.1 ± 11.2	28.9 ± 4.2			
Roth 2016 [20]	Alirocumab 75 Q2W	37	14	59.3 ± 11.3	29.7 ± 5.0	hypercholesterolemia at moderate-to-very-high CV risk	a maximally tolerated dose of statin	24
	Placebo	73	40	59.4 ± 10.2	32.3 ± 6.7			
Stroes 2016 [21]	Alirocumab 75 Q2W	116	69	62.5 ± 9.9	29.4 ± 5.6	hypercholesterolemia	no statin	24
	Placebo	58	31	63.1 ± 10.7	28.5 ± 4.6			
Teramoto 2016 [23]	Alirocumab 75/150 Q2W	144	84	60.3 ± 9.7	25.6 ± 4.3	HeFH or non-HeFH at high CV risk	stable dose of statin	52
	Placebo	72	47	61.8 ± 9.0	25.4 ± 3.2			
Koh 2018 [17]	Alirocumab 75 Q2W	97	83	61.2 ± 10.4	26.3 ± 4.0	hypercholesterolemia at high cardiovascular risk	stable dose of statin	24
	Placebo	102	81	60.1 ± 9.1	26.6 ± 3.8			
Schwartz 2018 [9]	Alirocumab 75 Q2W	9462	7072	58.5 ± 9.3	28.5 ± 4.9	recent ACS and inadequate lipid control	maximum tolerated dose of of statin	146
	Placebo	9462	7090	58.6 ± 9.4	28.5 ± 4.8			
Teramoto 2019 [22]	Alirocumab 150 Q2W	53	33	63.6 ± 10.4	26.4 ± 4.7	HeFH or non-FH	the lowest-strength dose of atorvastatin or a non-statin therapy	12
	Placebo	56	37	64.6 ± 10.0	25.6 ± 4.0			
Han 2020 [14]	Alirocumab 75/150 Q2W	407	315	58.8 ± 10.7	25.6 ± 3.7	hypercholesterolemia at high CV risk	a maximally tolerated statin dose	24
	Ezetimibe	206	146	58.3 ± 11.2	25.2 ± 3.0			

5. Conclusions

In conclusion, alirocumab therapy can effectively reduce the incidence of CV events and all-cause mortality. There was no significant difference in the incidence of AE in the alirocumab group compared to the control group. However, the impact of alirocumab on CV mortality is still inconclusive, and more long-term studies are needed to solve this issue.

Author contributions

WWT—extraction, analysis and interpretation of data, drafting of the manuscript; FZQ—analysis of data, manuscript revision; BJH—design and revision, statistical analysis; All—final approval of the manuscript submitted.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm2203093.

References

[1] Paone C, Diofano F, Park D, Rottbauer W, Just S. Genetics of Cardiovascular Disease: Fishing for Causality. Frontiers in Cardiovascular Medicine. 2018; 5: 60.
[2] Shara NM. Cardiovascular disease in Middle Eastern women. Nutrition, Metabolism, and Cardiovascular Diseases. 2010; 20: 412–418.
[3] Authors/Task Force Members:, Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, *et al.* 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016; 253: 281–344.
[4] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366: 1267–1278.
[5] Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, *et al.* Association between Lowering LDL-C and Cardiovascular Risk Reduction among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. Journal of the American Medical Association. 2016; 316: 1289–1297.
[6] Seidah NG, Awan Z, Chrétien M, Mbikay M. PCSK9: a key modulator of cardiovascular health. Circulation Research. 2014; 114: 1022–1036.
[7] Tibolla G, Norata GD, Artali R, Meneghetti F, Catapano AL. Proprotein convertase subtilisin/kexin type 9 (PCSK9): from structure-function relation to therapeutic inhibition. Nutrition, Metabolism, and Cardiovascular Diseases. 2011; 21: 835–843.
[8] Shapiro MD, Fazio S, Tavori H. Targeting PCSK9 for therapeutic gains. Current Atherosclerosis Reports. 2015; 17: 499.
[9] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, *et al.* Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. The New England Journal of Medicine. 2018; 379: 2097–2107.
[10] Casula M, Olmastroni E, Boccalari MT, Tragni E, Pirillo A, Catapano AL. Cardiovascular events with PCSK9 inhibitors: an updated meta-analysis of randomised controlled trials. Pharmacological Research. 2019; 143: 143–150.
[11] Dicembrini I, Giannini S, Ragghianti B, Mannucci E, Monami M. Effects of PCSK9 inhibitors on LDL cholesterol, cardiovascular morbidity and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. Journal of Endocrinological Investigation. 2019; 42: 1029–1039.
[12] Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R, *et al.* Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. European Heart Journal. 2015; 36: 1186–1194.
[13] Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, Baccara-Dinet MT, Lorenzato C, *et al.* Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dL or Higher. Cardiovascular Drugs and Therapy. 2016; 30: 473–483.
[14] Han Y, Chen J, Chopra VK, Zhang S, Su G, Ma C, *et al.* ODYSSEY EAST: Alirocumab efficacy and safety vs ezetimibe in high cardiovascular risk patients with hypercholesterolemia and on maximally tolerated statin in China, India, and Thailand. Journal of Clinical Lipidology. 2020; 14: 98–108.e8.
[15] Kastelein JJP, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, *et al.* ODYSSEY FH i and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. European Heart Journal. 2015; 36: 2996–3003.
[16] Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, *et al.* Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO i study. American Heart Journal. 2015; 169: 906–915.e13.
[17] Koh KK, Nam CW, Chao T, Liu M, Wu C, Kim D, *et al.* A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT). Journal of Clinical Lipidology. 2018; 12: 162–172.e6.
[18] Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, *et al.* Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. Journal of Clinical Lipidology. 2015; 9: 758–769.
[19] Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, *et al.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. The New England Journal of Medicine. 2015; 372: 1489–1499.
[20] Roth EM, Moriarty PM, Bergeron J, Langslet G, Manvelian G, Zhao J, *et al.* A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE i. Atherosclerosis. 2016; 254: 254–262.
[21] Stroes E, Guyton JR, Lepor N, Civeira F, Gaudet D, Watts GF, *et al.* Efficacy and Safety of Alirocumab 150 mg every 4 Weeks in Patients with Hypercholesterolemia not on Statin Therapy: the ODYSSEY CHOICE II Study. Journal of the American Heart Association. 2016; 5: e003421.
[22] Teramoto T, Kiyosue A, Ishigaki Y, Harada-Shiba M, Kawabata Y, Ozaki A, *et al.* Efficacy and safety of alirocumab 150 mg ev-

ery 4 weeks in hypercholesterolemic patients on non-statin lipid-lowering therapy or lowest strength dose of statin: ODYSSEY NIPPON. Journal of Cardiology. 2019; 73: 218–227.

[23] Teramoto T, Kobayashi M, Tasaki H, Yagyu H, Higashikata T, Takagi Y, *et al*. Efficacy and Safety of Alirocumab in Japanese Patients with Heterozygous Familial Hypercholesterolemia or at High Cardiovascular Risk with Hypercholesterolemia not Adequately Controlled with Statins–ODYSSEY JAPAN Randomized Controlled Trial. Circulation Journal. 2016; 80: 1980–1987.

[24] Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, *et al*. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. Journal of the American College of Cardiology. 2012; 60: 2631–2639.

[25] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, *et al*. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England Journal of Medicine. 2017; 376: 1713–1722.

[26] Steg PG, Szarek M, Bhatt DL, Bittner VA, Brégeault M, Dalby AJ, *et al*. Effect of Alirocumab on Mortality after Acute Coronary Syndromes. Circulation. 2019; 140: 103–112.

[27] Guedeney P, Giustino G, Sorrentino S, Claessen BE, Camaj A, Kalkman DN, *et al*. Efficacy and safety of alirocumab and evolocumab: a systematic review and meta-analysis of randomized controlled trials. European Heart Journal. 2019: ehz430.

[28] Turgeon RD, Tsuyuki RT, Gyenes GT, Pearson GJ. Cardiovascular Efficacy and Safety of PCSK9 Inhibitors: Systematic Review and Meta-analysis Including the ODYSSEY OUTCOMES Trial. The Canadian Journal of Cardiology. 2018; 34: 1600–1605.

[29] Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Faergeman G, *et al*. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. Atherosclerosis Supplements. 2004; 5: 81–87.