Frontiers in Economics and Management Volume 2 Issue 6, 2021
ISSN: 2692-7608 DOI: 10.6981/FEM.202106_2(6).0008

Meta-analysis of the Efficacy and Safety of PCSK9 Inhibitors in the Treatment of Atherosclerotic Cardiovascular Disease

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Abstract

Background: Proprotein convertase subtilisin/kexin type 9(PCSK9) inhibitors have been proven to be effective lipid-lowering agents, but for patients with atherosclerotic cardiovascular disease (ASCVD), their impact on the outcome of cardiovascular events is still not clear enough, so as its adverse events. We evaluated the efficacy and safety of PCSK9 inhibitors in the treatment of ASCVD through systematically reviewing and meta-analyzing randomized controlled trials. Methods: We searched Pubmed, Embase, Medline, Cochrane Library, CNKI, Wanfang Database, Chinese Biomedical Literature Database (CBM), screened articles, and meta-anlysised the outcomes on efficiency and safety aspect. Results: 9 RCT with a total of 53386 patients were included from 449 articles. Meta-analysis showed: (1) In the context of basic statin therapy, PCSK9 inhibitors can significantly reduce the incidence of major cardiovascular adverse events (MACE) compared with placebo [OR=0.83,95%CL(0.79,0.88), P<0.001]. and two individual components of MACE, non-fatal myocardial infarction [OR=0.79,95%CL (0.73,0.85), P<0.001], stroke [OR=0.79, 95%CL(0.73,0.85). But all-coused and cardiovascular death [OR=0.95, 95% CL (0.84, 1.08), P=0.43], unstable angina [OR=0.90, 95% CL (0.77, 1.07), P=0.23] had no significant difference. (2) Compared with placebo, PCSK9 inhibitor didnot increase the occurance of adverse reactions [OR=0.99,95%CL (0.90,1.09), P=0.88] and serious adverse reactions [OR=0.96,95%CL(0.92-1.00), P=0.06]. The use of PCSK9 inhibitors only increased minor adverse reactions, such as injection site reactions [OR=1.86, 95%CL (1.40, 2.47), P<0.001] and pain in extremity [OR=1.47, 95%CL (1.14-1.91), P=0.003], so as new diabetes, allergies, and neurocognitive events. Conclusion: PCSK9 inhibitors can effectively reduce the occurrence of cardiovascular adverse events without increasing the occurrence of adverse reactions and serious adverse reactions when used in ASCVD patients and on statin background therapy.

Keywords

Proprotein Convertase Subtilisin/ Kexin Type 9 Inhibitor; Atherosclerotic Cardiovascular Disease; Meta Analysis.

1. Introduction

Atherosclerotic Cardiovascular Disease (ASCVD) is the most common cardiovascular disease[1], and cholesterol is the most important and causal risk factor for ASCVD. At present, statins are still the gold standard therapy for lowering LDL cholesterol(LDL-C0 levels, but for some high-risk cardiovascular disease patients, statins may not reduce LDL-C to a statisfied level. For patients who are intolerant to statins or resistant to high-dose statins, the efficiency of statin is limited [2,3]. In recent years, Proprotein Convertase Subtilisin/Kexin Type 9, PSCK9 has entered people's attention because it can significantly reduce LDL-C levels and bring cardiovascular benefits further.

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PCSK9 inhibitor refers to a collection of drugs that inhibit the PCSK9. Amgen's evolocumab, Sanofi's alirocumab and Novartis' Inclisiran are currently on the market. The previous meta-analysis showed that PCSK9 inhibitors can significantly reduce LDL-C compared with placebo, with a Standard Mean Difference (SMD) of -50.7%[4]. In patients with high cholesterolemia, PCSK9 inhibits can reduce the occurance of myocardial infarction, stroke, and decreased coronary revascularization[5]. However, there are few studies on the cardiovascular outcomes of ASCVD patients. And there have been different conclusions from clinical trials on the adverse reactions such as myalgia, injection site reactions, and neurocognitive disorder. This article aims to systematically review and meta-analyse all available randomized controlled trials (RCTs) of PCSK9 inhibitors for ASCVD to assess their impact on cardiovascular outcomes and adverse events.

2. Method

The systematic review and meta-analysis was conducted according to the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) statement. We searched Pubmed, Embase, Medline, Cochrane Library, CNKI, Wanfang Database, China Biomedical Literature Database (CBM) from database inception to March 2021. The included studies were RCT trials of PSCK9 inhibitors (alirocumab, evolocumab or inclisiran) and the controlled group, and reported recardiovascular outcome indicators. Limit the patient to patients with atherosclerotic cardiovascular disease (at least one of acute coronary syndrome, hi story of myocardial infarction, stable or unstable angina, revascularization of coronary or other arteries, stroke or atients with clear cardiovascular risk), but no requirement for baseline LDL-C. Two independent reviewers initially screened the article based on the article title and abstract, and read the full text to determine whether to include it. We use the Cochrane quality evaluation tool [5] to evaluate quality of RCTs on 7 dimensions: sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential threats.

The main outcome is major adverse cardiovascular events (MACE), which is defined as a combination of all-cause or cardiovascular death, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, in unstable angina requiring hospitalization, and myocardial infarction. Secondary outcomes include all-cause mortality and individual MACEs. Safety outcomes include adverse events, serious adverse events, neurocognitive events, diabetes-related events, muscle pain, etc.

Use Review Manager version 5.3 to meta-analyse. The resultsare presented as odds ratios(OR) with 95% confidence interval(Ci). In consider of statistical heterogeneity, when I^2 <50%, the fixed effects model is used for analysis, otherwise the random utility model is chosen. And we assessed the bias of publications by the checking symmetry of the funnel chart.

3. Result

Nine RCTs were included from 449 articles, involving 53,514 patients. Table 1 shows a summary of key characteristics of included trials. Except for YUKAWA (2014), which is a six-arm test, the rest are two-arm studies. The YUKAWA trial included a test group of Evolocumab 140 mg Q2W with a similar dose to other studies and a control group of placebo Q2W.

Most of the patients included in these trials received the most tolerated statin. Under normal circumstances, the dose of alirocumab is 75 mg every 2 weeks. Based on the LDL-C response, the dose is increased to 150 mg in the second week. In the trial of evolocumab, the fixed dose of 140 mg every 2 weeks is 420 mg per month, inclisiran In the trial, 284 mg was injected on the 1st, 90th, 270th, and 450th days. The average follow-up time was 1.31 years. Nine RCTs all used double-blind randomized controls, and the quality of the literature was high, as shown in

ISSN: 2692-7608 DOI: 10.6981/FEM.202106_2(6).0008

Figure 1. However, 3 studies[10][13][14] reported incomplete results, missing data on the occurrence of serious adverse reactions, data on the occurrence of major cardiovascular adverse events, and patient baseline data.

Table 1. Characteristics of included trials

Trials	Cardiovascular-related inclusion criteria	Follow-up time	Number of cases		Age, Mean±SD		Female sex, %		Intervention	Background treatment
			T	C	T	C	T	C		
YUKAWA 2014[7]	Patients with high risk of cardiovascular events	12 weeks	52	52	60.8 ±9.2	60.2 ±10.1	45.1	30.8	T: Evolocumab 140 mg Q2W C: placebo	Stable statin therapy (±ezetimibe)
ODYSSEY COMBO I 2015[8]	Patients with risk of cardiovascular disease or coronary heart disease	24 weeks	205	106	63.0 ±9.5	63.0 ±8.8	37.3	28.0	T: Alirocumab 75/150mg Q2W C: placebo	MTD stable statin therapy
ODYSSEY LONG TERM 2015[9]	Patients confirmed coronary heart disease or with risk equivalent to coronary heart disease	78 weeks	1530	780	NR	NR	36.8	39.6	T: Alirocumab 150mg Q2W C: placebo	88.8% Medium to high intensity statin therapy
GLAGOV 2016[10]	Patients with stable coronary artery disease treated with statins	76 weeks	423	423	59.8 ±9.6	59.6 ±8.8	27.7	27.2	T: Evolocumab 420mg Q4W C: placebo	Statins (2.1% +ezetimibe)
FOURIER 2017[11]	Patients with ASCVD	2.2 years	13784	13780	62.5 ±9.1	62.5 ±8.9	24.6	24.5	T: Evolocumab 140 mg Q2W/ 420mg QM C: placebo	Statins (5.3% +ezetimibe)
ODYSSEY OUTCOMES 2018[12]	Patients who are admitted to hospital for acute coronary syndrome within 12 months	2.8 years	9443	9450	58.5 ±9.3	58.6 ±9.4	25.3	25.1	T: Alirocumab 75/150 mg Q2W C: placebo	83% MTD stable statin therapy
EVOPACS 2019[13]	Patients admitted to hospital due to coronary syndrome	8 weeks	155	153	60.5 ±12.0	61.0 ±10.7	17	20	T: Evolocumab 420mg Q4W C: placebo	high intensity statin therapy
ORION-10 2020[14]	Patients with ASCVD	540 days	781	780	66.4 ±8.9	65.7 ±8.9	32.5	29.7	T: Inclisiran: 284mg injection 4 times within 450 days C: placebo	Statins (+10% ezetimibe
ORION-11 2020[14]	Patients with ASCVD or in equivalent risk of ASCVD	540 days	810	807	64.8 ±8.3	64.8 ±8.7	28.5	28	T: Inclisiran: 284mg injection 4 times within 450 days C: placebo	Statins (+7% ezetimibe)

YUKAWA, Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk; ODYSSEY COMBO I, Efficacy and Safety of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; GLAGOV, GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; EVOPACS, Evolocumab for Early Reduction of LDL-cholesterol Levels in Patients With Acute Coronary Syndromes; ORION-10, Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol; ORION-11, Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol; T, test group; C,control group; Q2W, every 2 weeks; QM, once a month; MTD, Maximal Tolerable Dose.

3.1. Efficacy

3.1.1. MACE

Eight trials reported MACE. PCSK9 inhibitors significantly reduced the risk of MACE compared with control (Fig. 1, Table 2). And the outcomes did not differ among alirocumab, evolocumab and inclisiran.

ISSN: 2692-7608 DOI: 10.6981/FEM.202106_2(6).0008

3.1.2. Mortality

Eight trials reported cardiovascular mortality, and seven trials reported all-cause mortality. PCSK9 inhibitors did not reduce the risk of all-cause mortality or cardiovascular disease mortality. (Table 2)

3.1.3. Other cardiovascular outcomes

PCSK9 inhibitors can reduce the risk of myocardial infarction, stroke, and coronary revascularization, but the hospitalization rate for unstable angina pectoris is not significantly reduced. (Table 2)

Table 2. Summary of findings

Outcome	n	I^2	OR (95% CI)	P
MACE	53386	0%	0.83(0.79,0.88)	<0.001
Mortality				
All-cause	50358	43%	0.96(0.88-1.06)	0.46
Cardiovascular	53410	3%	0.95(0.84,1.08)	0.43
Myocardial infarction	53410	48%	0.79(0.73-0.85)	<0.001
Unstable angina	49924	44%	0.90(0.77-1.07)	0.23
Stroke	33671	31%	0.79(0.73-0.85)	<0.001
Coronary revascularization	22668	0%	0.87(0.79-0.95)	0.003
adverse events	53386	57%	0.99(0.90-1.09)	0.88
Serious adverse events	52664	0%	0.96(0.92-1.00)	0.06
Neurocognitive disorder	50232	21%	1.00(0.86 -1.15)	0.95
New-onset diabetes	49613	0%	0.99(0.92-1.06)	0.78
Local injection-site reaction	53510	60%	1.86(1.40-2.47)	<0.001
allergic	49386	0%	1.04(0.96-1.13)	0.33
Pain in extremity	5390	39%	1.47(1.14-1.91)	0.003

MACE, major adverse cardiovascular events; n, number; OR, odds ratio; CI, confidence interval; P, P-value.

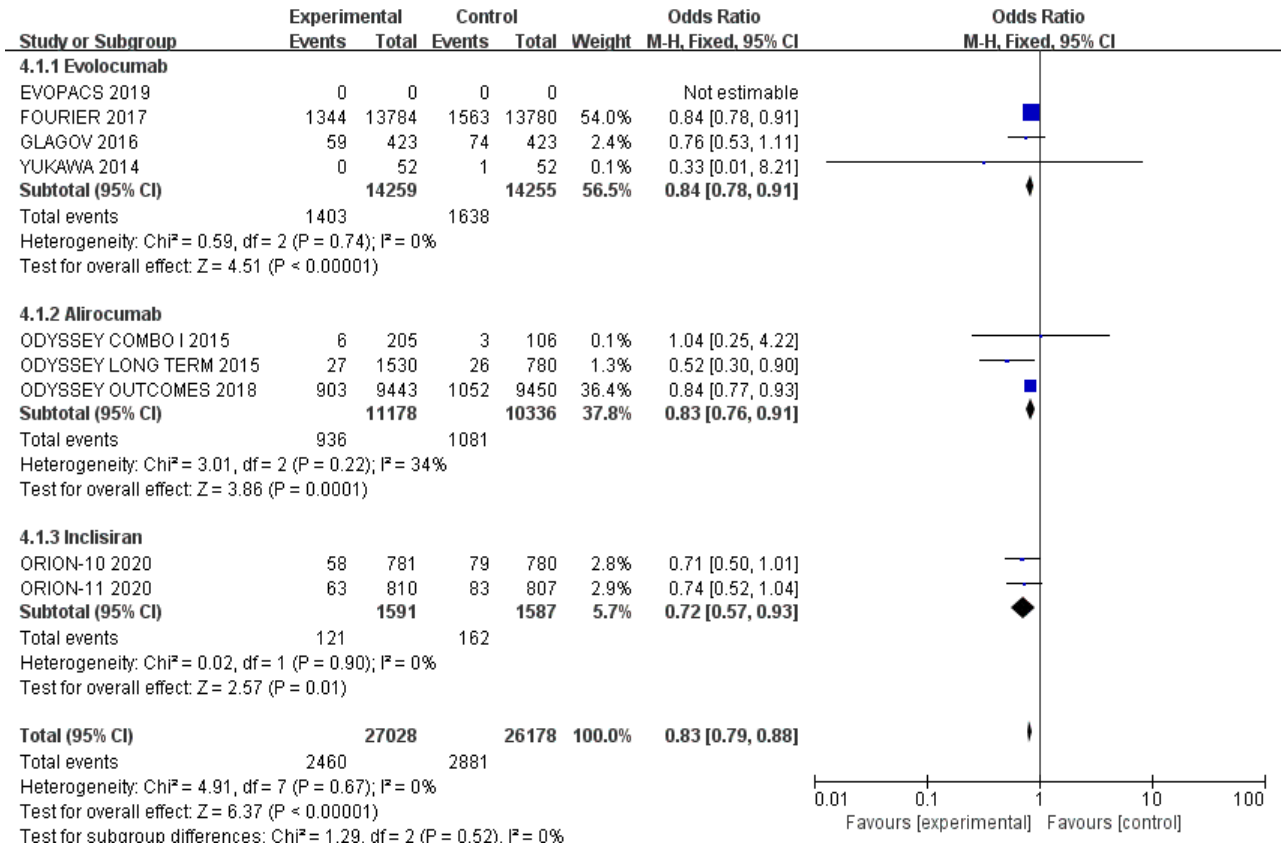

Figure 1. Meta-analysis of major adverse cardiovascular events

ISSN: 2692-7608 DOI: 10.6981/FEM.202106_2(6).0008

3.2. Safety

Compared with placebo, PCSK9 inhibitors did not increase adverse events, serious adverse events, neurocognitive events and diabetes-related events, but significantly increased the occurrence of limb pain and injection site reactions. (Table 2)

3.3. Publication bias

The funnel chart is used to analyze the publication bias of major cardiovascular adverse events and adverse events. The funnel chart is more symmetrical, indicating that the publication bias is less likely.

4. Discussion

4.1. Overview of the results

In this meta-analysis of 9 RCTs, the incidence of MACE was significantly lower in the PCSK9 inhibitor group (2460 [9.1%] of 27028 patients) than in the placebo group (2881 [11.0%] of 26178 patients; odds ratio [OR] 0.83, 95% CI 0.79–0.88; p<0.0001). The use of PCSK9 inhibitors did not increase the incidence of serious adverse events, but the incidence of injection site reflection and limb pain in the PCSK9 inhibitor group was higher than that of placebo group.

Compared with the previous meta-analysis[15][16], we focused on ASCVD population, and paid more attention to cardiovascular outcome indicators. And included the results of two inclisiran RCTs published in 2020 that were not incluede by the previous review.

4.2. Accessibility of PCSK9 inhibitors

The high price of PCSK9 inhibitors hinders their use in clinical practice. The current cost in the United States is US$5,850 per person per year, which is much higher than other lipid-lowering treatment options. Cost-effectiveness analysis carried out in developed and developing countries have shown that it must take a substantial price reduction to be cost-effective[17][18].

4.3. Limitation

First of all, the results of the two largest trials, FOURIER and ODYSSEY OUTCOMES, accounted for 90.4% of the weight, which largely affected the efficacy and safety estimates. Second, the trial follow-up time is generally short (the longest trial median follow-up time is 2.8 years), so the long-term effects of PCSK9 inhibitors are still unknown.

5. Conclusion

PCSK9 inhibitors can reduce the risk of MACE, but the effect on mortality is unclear. During the treatment, there were no serious adverse events, only minor adverse events. Currently, cost limits the use of PCSK9 inhibitors in clinical practice.

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