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Review Article

Application Value of PCSK9 Inhibitor in Cardiovascular High Risk Patients: A Meta-Analysis

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Abstract

Background: Proprotein convertase subtilisin / Kexin type 9 (PCSK9) inhibitors are efficacious lipid-lowering agents. This drug is related to improving the prognosis of patients with cardiovascular disease (CVD). The purpose of this meta-analysis was to systematically analyze the safety and efficacy of PCSK9 inhibitors in all published randomized controlled trials (RCTs).

Methods: As of October 25, 2021, we searched PubMed, EMBASE, MEDLINE, Cochrane Library and web of science.

Results: From 684 articles, we included 11 trials for meta-analysis, including 52511 participants (26938 in the PCSK9 inhibitor group and 25573 in the control group). In terms of effectiveness, PCSK9 inhibitors reduced the risk of major adverse cardiovascular events(MACE) (OR=0.89, 95% Cl: 0.83-0.95, *P*=0.0009), but did not significantly reduce the risk of cardiovascular death (OR=0.95, 95% Cl: 0.84-1.07, *P*=0.38) or all-cause death (OR=0.93, 95% Cl: 0.85-1.03, *P*=0.18); In terms of safety, PCSK9 did not increase the risk of treatment-emergent adverse events (TEAE)(OR=0.98, 95% Cl: 0.94-1.02, *P*=0.28).

Conclusion: PCSK9 inhibitors can significantly reduce the risk of MACE in patients with high cardiovascular risk, which is well tolerated, but the impact on the risk of death is unclear.

Keywords: Cardiovascular risk; Adverse events; Proprotein convertase 9; Alirocumab; Evolocumab

Introduction

Ischaemic stroke is one of the leading causes of death, dementia and disability in the developed world. The gold standard intervention is carotid endarterectomy (CEA) The prespecifified analyses designed to assess the effect of PCSK9 inhibitors on stroke demonstrated a reduction in risk of ischemic stroke (IS) without increasing hemorrhagic stroke PCSK9 inhibitor is an all human monoclonal antibody, which can specifically bind to the pro protein convertase subtilisin / Kexin type 9 (PCSK9) with high affinity (1).

By inhibiting the binding of PCSK9 to low-density lipoprotein receptors, it can increase the number of low-density lipoprotein receptors on the surface of hepatocytes, so as to promote the degradation of LDL-C and reduce the level of LDL-C in blood (2). A large number of scientific studies have repeatedly confirmed that dyslipidemia, especially the increase of LDL-C, is

the most important pathogenic risk factor for the occurrence of atherosclerotic cardiovascular disease (ASCVD) (3-9). At present, PCSK9 inhibitors mainly include alirocumab and evolocumab. Bococizumab is also a PCSK9 inhibitor, but Pfizer has stopped relevant research and this paper has not included its relevant literature. In recent years, a large number of data from RCTs of evolocumab and alirocumab have evaluated the impact of PCSK9 inhibitors on cardiovascular events. Ricky DT, Manuela C and others have done similar meta-analysis (10,11). It indicated that patients with cardiovascular diseases have obvious clinical significance benefit, safe and effective (12). Although, due to the variety of literature research populations included (including cardiovascular high-risk population, patients with simple hyperlipidemia and statin intolerance, etc.) Therefore, there is an urgent need to systematically evaluate the efficacy and safety of PCSK9 inhibitors in cardiovascular high-risk patients.

Our purpose was to systematically review and meta-analyze all current RCTs of PCSK9 inhibitors in cardiovascular high-risk patients to evaluate its effects on MACE, cardiovascular death, TEAE and so on.

Methods

As of October 2021, we searched PubMed, EMBASE, MEDLINE, Cochrane Library and web of science. Not limited to languages. Search for the following keywords: "alirocumab", "evolocumab", "AMG145", "REGN727", "sar236553", "randomized controlled trial", "clinical trial", "intervention study", "coronary heart disease(CHD)", "atherosclerotic cardiovascular disease(ASCVD)", "acute coronary syndrome(ACS)" and "ischemic heart disease(IHD)", "nonhemorrhagic stroke", "peripheral artery disease(PAD)". We also manually searched the references of these studies. For the literature that may have data but not provided in the original text, I even contacted the author of the literature. We excluded the trials of bococizumab.

Two researchers independently screened the title and abstract of the article, and used Cochrane handbook (12) to evaluate the quality of the literature. The two researchers independently extracted the data in the article. When the extracted data were inconsistent, they negotiated and checked, and when the opinions were inconsistent, they were judged by the third party. The extracted data included: 1) basic data of the patient (gender, age, population characteristics), background therapy, sample size, follow-up time, intervention measures, etc. (Table 1); 2) Effectiveness evaluation: the primary endpoint is MACE (a composite of cardiovascular death, nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalization for unstable angina), the secondary endpoints were all-cause death, cardiovascular death, nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalization for unstable angina, coronary artery and other vascular revascularization; Safety evaluation: the primary endpoint is TEAE; secondary endpoints: serious adverse events (SAE), TEAEs leading to discontinuation, injection site reaction, neurocognitive disorders, Diabetes in patients with no history of diabetes or worsening of diabetes in patients with history of diabetes, Arthralgia or Myalgia, Alanine aminotransferase(ALT) or Aspartate aminotransferase(AST)>3 times upper limit of normal value(ULN) and creatine kinase(CK)>5ULN.

Inclusion criteria: 1) randomized controlled trial; 2) the study population is patients with CHD or CHD risk equivalents, including CHD, nonhemorrhagic stroke, PAD, etc.; 3) compare PCSK9 inhibitor group with control group; 4) Report the data of MACE, cardiovascular death or all-cause death, SAE, etc.; 5) follow up for more than 8 weeks.

Exclusion criteria: 1) studies and case reports published in the form of abstracts; 2) non-human studies; 3) lack of studies in the control group.

Revman5.3 software provided by Cochrane Collaboration website was used to analyze the data. The heterogeneity test was conducted by calculating I2. If I2<50%, indicating no statistical heterogeneity or small heterogeneity, the fixed effect model was used for analysis; if I2 ≥ 50%, indicat-

ing large heterogeneity, the random effect model was used for analysis. The dichotomous variables were expressed by odds ratio (OR) and its corresponding 95% Cl.

Table 1: Eleven literatures were included, including 52511 patients

Trials	*Sample size*	*Duration*	*Gender, %M*	*Mean age, years*	*PCSK9 inhibitor group*	*Control group*	*Patient Population*	*Background*
1.EVOPACS, 2019, NCT03287609 (6)	155/153	8weeks	128(83)/123(80)	60.5±12.0/61.0±10.7	Evolocumab(420mg monthly)	Placebo	ACS [NSTE-ACS with symptom onset <72h or STEMI with symptom onset <24h before screening]	statins
2.FOURIER, 2017, NCT01764633 (7)	13784/13780	2.2years	10,397(75.4)/10,398(75.5)	62.5±9.1/62.5±8.9	Evolocumab(140mg every 2 weeks /420mg monthly)	Placebo	ASCVD (a history of MI, nonhemorrhagic stroke, or symptomatic PAD, as well as additional characteristics that placed them at higher cardiovascular risk)	statins
3.GLAGOV, 2016, NCT01813422 (8)	484/484	76weeks	349(72.1)/350(72.3)	59.8±9.6/59.8 ±8.8	Evolocumab(420mg monthly)	Placebo	at least 1 epicardial coronary stenosis of 20% or greater on clinically indicated coronary angiography	statins
4.ODYSSEY COMBO I, 2014, NCT01644175 (9)	209/107	52weeks	131(62.7)/77 (72.0)	63.0 ±9.5/63.0±8.8	Alirocumab(75-150mg every 2 weeks)	Placebo	1. CVD with LDL-C ≥70 mg/dL; 2.coronary heart disease(CHD) with LDL-C≥100mg/dL;	statins
5.ODYSSEY COMBO II, 2015, NCT01644188. (10)	479/241	52weeks	360(75.2)/170 (70.5)	61.7±9.4/61.3±9.2	Alirocumab(75-150mg every 2 weeks)	Ezetimibe	1.CVD with LDL-C≥1.8 mmol/L (≥70 mg/dL) 2.high cardiovascular risk with LDL-C≥2.6mmol/L(≥100 mg/dL);	Statins+stable diet(NCEP ATP III)
6.ODYSSEY EAST, 2020, NCT02715726 (11)	302/153	24weeks	234(77.2)/107(69.9)	59.8±10.8/58.8±11.1	Alirocumab(75-150mg every 2 weeks)	ezetimibe	CHD or CHD risk equivalents	statins
7.ODYSSEY J-IVUS, 2019, NCT02984982 (12)	93/89	36weeks	74(79.6)/72(80.9)	61.8±10.2/60.5±11.6	Alirocumab(75-150mg every 2 weeks)	SoC	ACS with LDL-C ≥2.59mmol/L (≥100mg/dL)	statins
8.ODYSSEY LONG TERM, 2015, NCT01507831. (13)	1553/788	78weeks	983(63.3)/474 (60.2)	60.4±10.4/60.6±10.4	Alirocumab(150mg every 2 weeks)	Placebo	Cardiovascular history and risk factors; LDL>70mg/dL (1.8mmol/L)	statins
9.ODYSSEY OUTCOMES, 2018, NCT01663402 (14)	9462/9462	2.8years.	7072(74.7)/7090(74.9)	58.5±9.3/58.6±9.4	Alirocumab(75mg every 2 weeks)	Placebo	ACS with LDL-C>70mg/dL(1.8 mmol /L)	statins
10.YUKAWA-1, 2014, NCT01652703 (15)	205/102	12weeks	121(59)/72(70.6)	61.9±9.6/60.5±9.9	Evolocumab(140mg every 2 weeks/ 420mg monthly)	Placebo	high risk for cardiovascular events.	statins
11.YUKAWA-2, 2016, NCT01953328 (16)	202/202	12weeks	121(60%)/123 (61%)	62±11/61±10	Evolocumab(140mg every 2 weeks/ 420mg monthly)	Placebo	high risk for CV events	statins

ASCVD: Atherosclerotic cardiovascular disease; CHD: coronary heart disease; ACS: Acute coronary syndrome; CVD: Cardiovascular disease; MI: myocardial infarction; PAD: peripheral artery disease; STEMI: ST-elevation myocardial infarction; NSTE-ACS: Non-ST-elevation ACS; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; SoC: standard of care (atorvastatin≥10mg/day or rosuvastatin≥5mg/day)

By drawing the "forest plot" to evaluate the efficacy and safety of PCSK9 inhibitor, $P < 0.05$ indicates that the difference is statistically significant. If the heterogeneity I2 > 50%, subgroup

analysis shall be carried out to analyze the source of heterogeneity, and sensitivity analysis shall be carried out by excluding the literature one by one to judge whether the meta-analysis results are robust. Publication bias was assessed by visual funnel plot symmetry.

Results

Search results and basic characteristics of included literature

After a comprehensive search, 684 relevant literatures were obtained, 153 duplicate literatures were preliminarily removed by endnote software, and the inconsistent literatures were excluded by reading the title, abstract and full text. A total of 11 literatures were included, including 52511 patients (Table 1). Participants in the trial were cardiovascular high-risk groups. (Fig. 1) summarizes the main characteristics of the participants. Patients in alirocumab group were given 75 mg every two weeks, and the dose was adjusted to 150mg every two weeks according to the reduction of LDL-C; Patients in the evolocumab group were given a fixed dose of 140 mg every 2 weeks or 420 mg per month. The follow-up time ranged from 8 weeks to 2.8 years. Included RCTs usually have a low or ambiguous risk of bias.

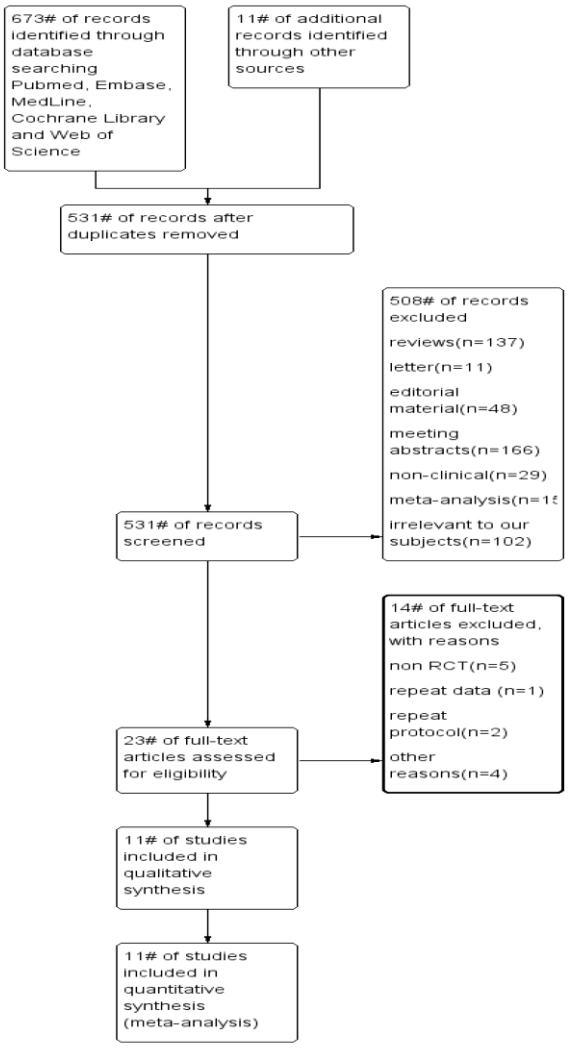

Fig. 1: cardiovascular high-risk groups

Effectiveness

Primary endpoint: major adverse cardiovascular events (MACE)

A total of 10 studies (13-21,23) reported major adverse cardiovascular events, including 26733 participants in the PCSK9 inhibitor group and 25471 participants in the control group. We found that compared with the control group, PCSK9 inhibitor treatment significantly reduced the incidence of MACE in patients with high cardiovascular risk, I2 = 34%, using the fixed effect model, OR=0.89, 95% Cl: 0.83-0.95, *P* = 0.0009 (Fig. 2a). By observing the funnel plot, the two sides were more opposite to each other, considering that there was no obvious publication bias (Fig. 2b).

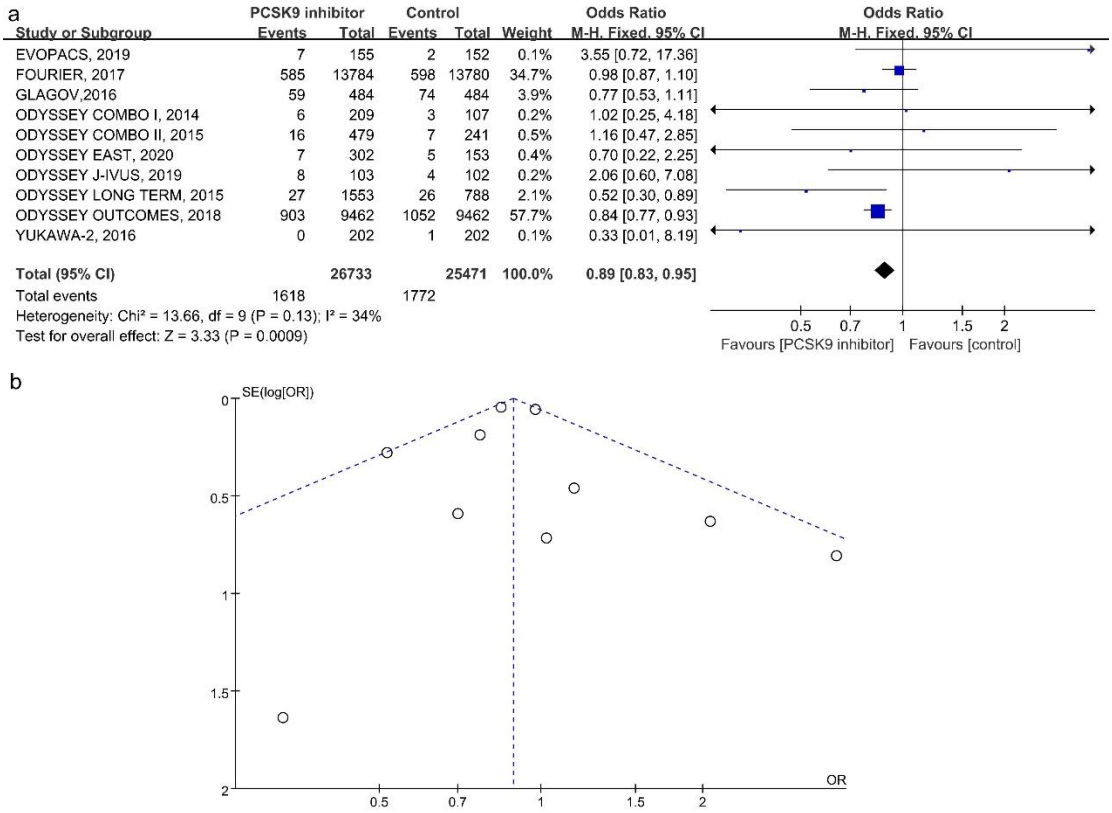

Fig. 2: Major adverse cardiovascular events (MACE).
a: using the fixed effect model, OR=0.89, 95% Cl: 0.83-0.95, *P* = 0.0009.
b: observing the funnel plot, the two sides are more opposite to each other, considering that there is no obvious publication bias

Nine trials (13-21) reported nonfatal myocardial infarction events. PCSK9 inhibitor could significantly reduce the risk of nonfatal myocardial infarction, I2 = 37%, OR=0.79, 95% Cl: 0.73-0.86, *P*<0.00001 (Fig. 3a), with obvious publication bias (Fig. 3b). 9 trials (13-21) reported fatal or nonfatal stroke events. PCSK9 inhibitor could significantly reduce the risk of nonfatal stroke. I2 = 0%, OR = 0.78, 95% Cl: 0.68-0.91, *P* = 0.001, with significant publication bias (Fig. 3a); 10 trials (13-22) reported coronary artery and other vascular revascularization events. PCSK9 inhibitor could significantly reduce the risk of revascularization of coronary artery and other vessels, I2 = 12%, OR = 0.82, 95% Cl: 0.77-0.88, *P* < 0.00001, with certain publication bias (Fig. 3b). 9 trials (13-

21) reported cardiovascular death events. The application of PCSK9 inhibitor could not reduce cardiovascular mortality I2 = 17%, or = 0.95, 95% Cl: 0.84-1.07, *P* = 0.38 (Fig. 4a), with obvious publication bias (Fig. 4b); 10 trials (13-21) reported all-cause death events, which also could not significantly reduce the risk of all-cause death. I2 = 38%, OR = 0.93, 95% Cl: 0.85-1.03, *P* = 0.18, with obvious publication bias (Fig. 4a). 8 trials (13-18,20,21) reported hospitalization for unstable angina events. PCSK9 inhibitor could not reduce the risk of hospitalization for unstable angina. I2 = 16%, OR = 0.90, 95% Cl: 0.76-1.06, *P* = 0.21, with obvious publication bias (Fig. 4b). Five trials (14,16,17,20,21) reported hospitalization for congestive heart failure events. PCSK9 inhibitor could not reduce the risk of hospitalization for congestive heart failure. I2 = 0%, OR = 0.94, 95% Cl: 0.81-1.10, *P* = 0.44, with obvious publication bias.

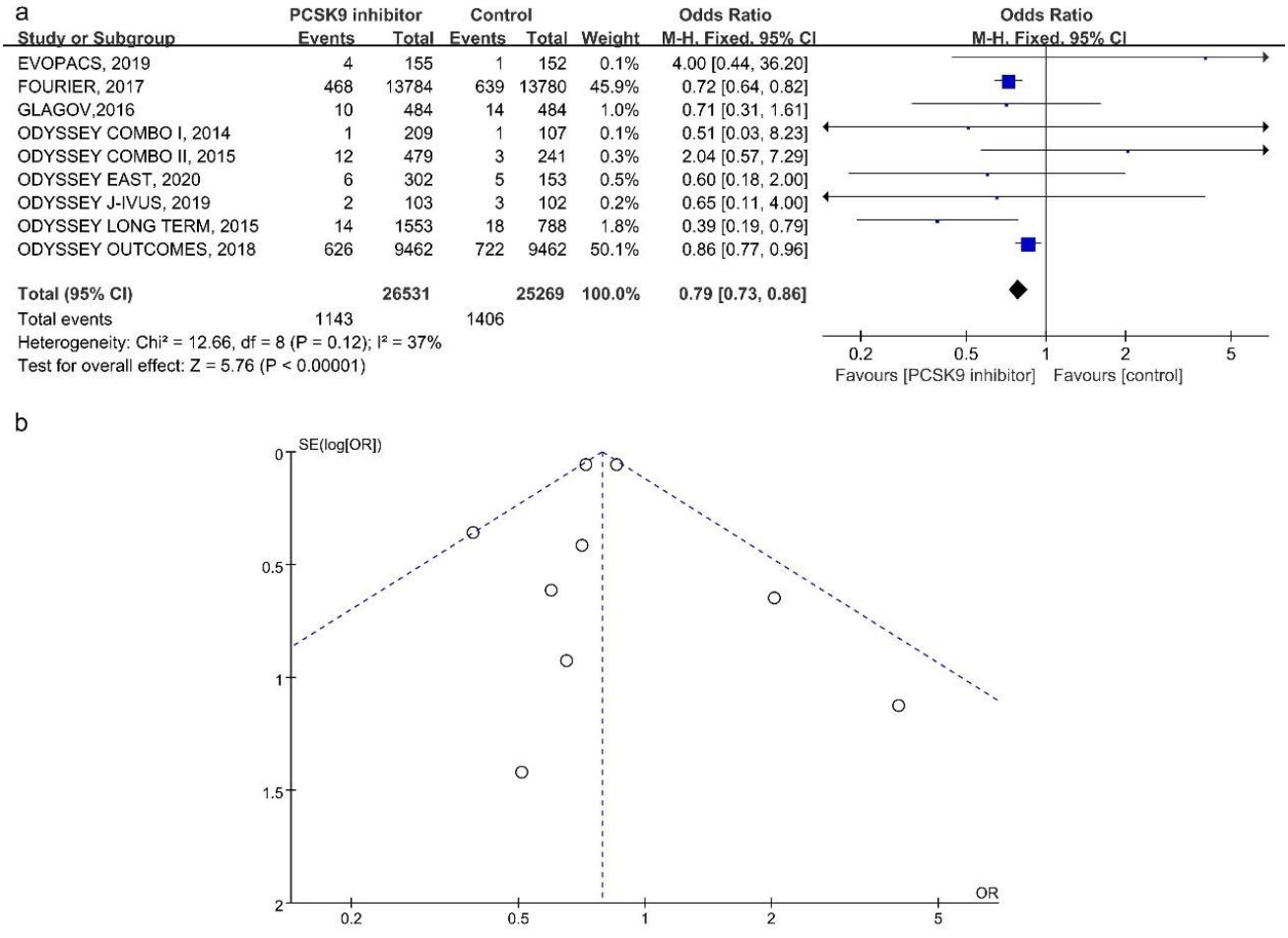

Fig. 3: PCSK9 inhibitor and the risk of nonfatal stroke.

a: PCSK9 inhibitor can significantly reduce the risk of nonfatal stroke. I2 = 0%, OR = 0.78, 95% Cl: 0.68-0.91, *P* = 0.001

b: PCSK9 inhibitor can significantly reduce the risk of revascularization of coronary artery and other vessels, I2 = 12%, OR = 0.82, 95% Cl: 0.77-0.88, *P* < 0.00001, with certain publication bias

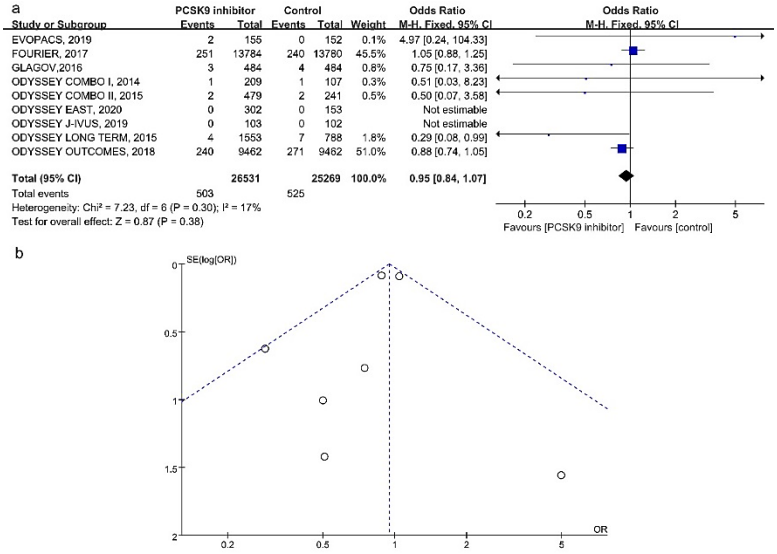

Fig. 4: PCSK9 inhibitor and the cardiovascular disease mortality

a: PCSK9 inhibitor cannot reduce cardiovascular disease mortality, I2=17%, OR=0.95, 95%Cl: 0.84-1.07, *P*=0.38.

b: obvious publication bias

Safety

Treatment-emergent adverse events(TEAE)

Eleven trials (6-16) reported TEAE. There was no significant difference in the risk of TEAE in the PCSK9 inhibitor treatment group (26938 participants) compared with the control group (25573 participants), I2 = 44%, using the fixed effect model OR = 0.98, 95% Cl: 0.94-1.02, *P* = 0.28 (Fig. 5a), A certain publication bias was found by observing the funnel diagram (Fig. 5b).

Using the literature exclusion method one by one, it is found that when the test data of ODYSSEY J-IVUS (19) was excluded, I2 = 30%, and the heterogeneity was significantly reduced, indicating that this test might be the main source of heterogeneity. The biggest difference between this test and other experiments was that the standard of care group (SoC) did not receive placebo injection, so there was no injection site reaction.

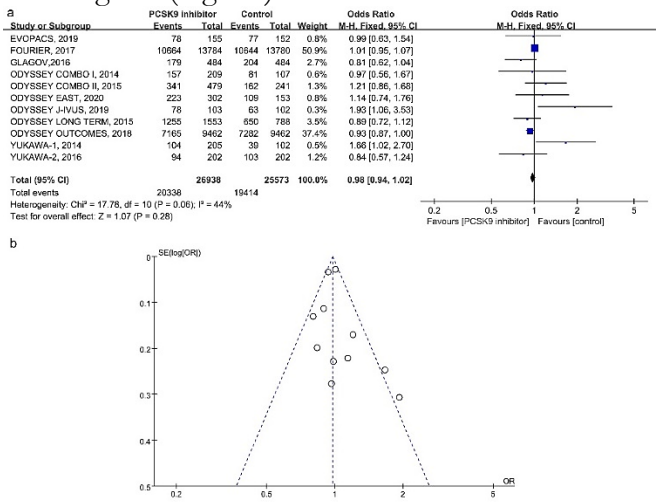

Fig. 5: Treatment-emergent adverse events(TEAE)

a: there was no significant difference in the risk of TEAE in the PCSK9 inhibitor treatment group (26938 participants) compared with the control group (25573 participants)

b: certain publication bias was found by observing the funnel diagram

However, when comparing injection site reaction events (13-23), there was a significant statistical difference in the incidence of injection site reaction events between the two groups, I2 = 0%, OR = 1.59, 95% Cl: 1.41-1.78, $P < 0.00001$, indicating that injection of PCSK9 inhibitor will bring obvious injection site reaction to patients. There was a certain publication bias by observing the funnel plot.

Discussion

In order to further explore the efficacy and safety of PCSK9 inhibitors in cardiovascular high-risk patients, this paper conducted a meta-analysis of 11 RCTs that met the inclusion criteria, involving 52511 patients. The results showed that PCSK9 inhibitor could significantly reduce MACE, especially the risk of nonfatal myocardial infarction, fatal or nonfatal stroke and revascularization (Fig. 2,3), but did not reduce the risk of all-cause death, cardiovascular death, hospitalization for unstable angina and congestive heart failure (Fig. 4); Except injection site reactions, PCSK9 inhibitors did not increase the risk of TEAE, SAE, TEAEs leading to discontinuation, neurocognitive disorders, diabetes in patients with no history of diabetes or worsening of diabetes in patients with history of diabetes, Arthralgia or Myalgia, AST/ALT>3ULN and CK>5ULN (Fig. 5). It shows that PCSK9 inhibitor is safe and effective in patients with high cardiovascular risk, and the patient's tolerance is good.

Firstly, this meta-analysis excluded clinical studies on statin intolerance and hyperlipidemia. The included studies were all trials on the application of PCSK9 inhibitors in high-risk cardiovascular patients, which reduced the statistical heterogeneity to a certain extent (the heterogeneity I2<50% in this meta-analysis). Secondly, most of the previous meta-analyses included RCTs implemented in European and American countries, and most of them were Caucasians, while we increased the research from Asian populations (18,22,23). At the same time, we excluded the trials of bococizumab (24) (Pfizer has stopped the development of the drug).

This meta-analysis shows that PCSK9 inhibitors cannot significantly reduce the risk of cardiovascular death and all-cause death in patients with high cardiovascular risk. The reasons for this result may be ① Insufficient RCTs and too small sample size; ② Most clinical trials were followed up for a short time, and cardiovascular death and all-cause death were not observed during the trial. Perhaps with the extension of drug application time, we can observe a significant reduction in cardiovascular mortality and all-cause mortality in patients with high cardiovascular risk. In addition, PCSK9 inhibitor failed to reduce the risk of hospitalization for unstable angina and congestive heart failure, which may be due to ① For several experiments included in this analysis, it should be noted that cardiovascular outcomes are not the primary endpoint designed by them. The non-fatal outcomes in the experimental process may occur repeatedly in the same patient and recorded for many times. The result is to greatly increase the harmful effects of drugs and reduce their beneficial effects on patients; ② The onset of unstable angina pectoris is closely related to plaque damage or plaque rupture. PCSK9 inhibitor can reduce the regression of percent atheroma volume and total atheroma volume, but cannot reduce the calcium, fibrous, fibrofatty, and necrotic volumes (25).

It must be admitted that although we conduct evaluation and analysis in strict accordance with the methods recommended in the Cochrane system evaluation manual, there are inevitably the following deficiencies: the follow-up time of the included studies is uneven, and the shortest follow-up time is only 8 weeks; There is a large gap between the maximum sample size and the minimum sample size; Most of the included studies were implemented in European and American countries, and most of them were Caucasian. The sample size of Asian clinical studies was too small and the proportion was too low; For evolocumab, Chinese patients need to spend about 7000-8000 dollars a year; For alirocumab, $4600-

9300 is required, which is also an important reason for limiting the number of patients participating in the experiment (26,27). Most of the results of this meta-analysis have obvious publication bias. The analysis reason is that the sample size of the two trials (14,21) accounts for too much.

Conclusion

PCSK9 inhibitor could greatly reduce the risk of MACE in patients with high cardiovascular risk, especially the risk of nonfatal myocardial infarction, nonfatal stroke and cardiovascular revascularization, which is relatively safe. The incidence of injection site reactions is high, while the incidence of other adverse events such as TEAE and SAE in PCSK9 inhibitor group is similar to that of the control group. However, the impact on mortality is not clear. In addition, drug cost is also an important factor limiting the number of clinical trial participants.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Barale C, Melchionda E, Morotti A, Russo I (2021). PCSK9 Biology and Its Role in Atherothrombosis. *Int J Mol Sci*, 22(11):5880.
2. Sabatine MS (2019). PCSK9 inhibitors: clinical evidence and implementation. *Nat Rev Cardiol*, 16(3):155-165.
3. Borén J, Chapman MJ, Krauss RM, et al (2020). Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*, 41(24):2313-2330.
4. O'Donoghue ML, Fazio S, Giugliano RP, et al (2019). Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. *Circulation*, 139(12):1483-1492.
5. Jang AY, Lim S, Jo SH, Han SH, Koh KK (2021). New Trends in Dyslipidemia Treatment. *Circ J*, 85(6):759-768.
6. Muraki I (2021). Role of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) on Lipid Metabolism and Insulin Resistance in Human. *J Atheroscler Thromb*, 28(4):317-318
7. Hamamura H, Adachi H, Enomoto M, et al (2021). Serum Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is Independently Associated with Insulin Resistance, Triglycerides, Lipoprotein (a) Levels but not Low-Density Lipoprotein Cholesterol Levels in a General Population. *J Atheroscler Thromb*, 28(4):329-337.
8. Shahreyar M, Salem SA, Nayyar M, George LK, Garg N, Koshy SKG (2018). Hyperlipidemia: Management with Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors. *J Am Board Fam Med*, 31(4):628-634.
9. Spolitu S, Dai W, Zadroga JA, Ozcan L (2019). Proprotein convertase subtilisin/kexin type 9 and lipid metabolism. *Curr Opin Lipidol*, 30(3):186-191.
10. Turgeon RD, Tsuyuki RT, Gyenes GT, Pearson GJ (2018). Cardiovascular Efficacy and Safety of PCSK9 Inhibitors: Systematic Review and Meta-analysis Including the ODYSSEY OUTCOMES Trial. *Can J Cardiol*, 34(12):1600-1605.
11. Casula M, Olmastroni E, Boccalari MT, Tragni E, Pirillo A, Catapano AL (2019). Cardiovascular events with PCSK9 inhibitors: an updated meta-analysis of randomised controlled trials. *Pharmacol Res*, 143:143-150.

12. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J (2019). Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*, 10:ED000142.
13. Koskinas KC, Windecker S, Pedrazzini G, et al (2019). Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS). *J Am Coll Cardiol*, 74(20):2452-2462.
14. Sabatine MS, Giugliano RP, Keech AC, et al (2017). Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*, 376(18):1713-1722.
15. Nicholls SJ, Puri R, Anderson T, et al (2016). Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA*, 316(22):2373-2384.
16. Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, Colhoun HM (2015). 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. *Am Heart J*, 169(6):906-915.e13.
17. Cannon CP, Cariou B, Blom D, et al (2015). 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. *Eur Heart J*, 36(19):1186-94.
18. Han YL, Ma YY, Su GH, et al (2020). [Efficacy and safety of alirocumab versus ezetimibe in high cardiovascular risk Chinese patients with hyperlipidemia: ODYSSEY EAST Study-Chinese sub-population analysis]. *Zhonghua Xin Xue Guan Bing Za Zhi*, 48(7):593-599.
19. Ako J, Hibi K, Tsujita K, et al (2019). Effect of Alirocumab on Coronary Atheroma Volume in Japanese Patients with Acute Coronary Syndrome - The ODYSSEY J-IVUS Trial. *Circ J*, 83(10):2025-2033.
20. Robinson JG, Farnier M, Krempf M, et al (2015). Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*, 372(16):1489-99.
21. Schwartz GG, Steg PG, Szarek M, et al (2018). Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*, 379(22):2097-2107.
22. Hirayama A, Honarpour N, Yoshida M, Yamashita S, Huang F, Wasserman SM, Teramoto T (2014). Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk--primary results from the phase 2 YUKAWA study. *Circ J*, 78(5):1073-82.
23. Kiyosue A, Honarpour N, Kurtz C, Xue A, Wasserman SM, Hirayama A (2016). A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk. *Am J Cardiol*, 117(1):40-7.
24. Ballantyne CM, Neutel J, Cropp A, et al (2015). Results of bococizumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, from a randomized, placebo-controlled, dose-ranging study in statin-treated subjects with hypercholesterolemia. *Am J Cardiol*, 115(9):1212-21.
25. Nicholls SJ, Puri R, Anderson T, et al (2018). Effect of Evolocumab on Coronary Plaque Composition. *J Am Coll Cardiol*, 72(17):2012-2021.
26. Fonarow GC, van Hout B, Villa G, Arellano J, Lindgren P (2019). Updated Cost-effectiveness Analysis of Evolocumab in Patients With Very High-risk Atherosclerotic Cardiovascular Disease. *JAMA Cardiol*, 4(7):691-695.
27. Bhatt DL, Briggs AH, Reed SD, et al (2020). Cost-Effectiveness of Alirocumab in Patients With Acute Coronary Syndromes: The ODYSSEY OUTCOMES Trial. *J Am Coll Cardiol*, 75(18):2297-2308.