OPEN

The benefits of PCSK9 inhibitors in patients with acute coronary syndrome: a systematic review and meta-analysis

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Abstract

Background: Proprotein convertase subtilisin/kexin 9 (PSCK9) inhibitors have been beneficial for many patients with hyperlipidemia. The objective of this study was to investigate the benefit of PSCK9 inhibitors in patients with acute coronary syndrome (ACS).

Methods: We systematically searched PubMed, EMBASE, and Cochrane Clinical Trials (published before January 2023; no language restriction) to compare the treatment of patients with ACS using PCSK9 inhibitors and placebo. The primary end points were major adverse cardiovascular events, nonfatal myocardial infarction, cardiogenic death, stroke, hospitalization for recurrent ACS, and coronary revascularization. Fixed- or random-effects models were used to assess the aggregated data.

Results: Of the 1686 identified studies, 5 were eligible and included in our analysis (of a total of 38,005 participants, 18,609 cases were placed in the PCSK9 inhibitor treatment group and 19,396 cases in the placebo group). Compared with the placebo group, PCSK9 inhibitors significantly reduced the major adverse cardiovascular events (odds ratio [OR]: 0.83; 95% confidence interval [CI]: 0.77–0.88; $P < 0.00001$) for patients following ACS. The incidence of nonfatal myocardial infarction (relative risk: 0.80; 95% CI: 0.74–0.87; $P < 0.00001$), cardiovascular death (OR: 0.96; 95% CI: 0.83–1.10; $P = 0.56$), stroke (OR: 0.74; 95% CI: 0.63–0.88; $P = 0.0007$), hospitalization for recurrent ACS (OR: 0.57; 95% CI: 0.40–0.83; $P = 0.003$), or coronary revascularization (OR: 0.82; 95% CI: 0.76–0.88; $P < 0.00001$) all demonstrated a significant decrease in the comparison between the 2 groups.

Conclusion: This meta-analysis demonstrated that treatment with PCSK9 inhibitors in patients with ACS reduced the probability of multiple cardiovascular events and improved patient prognosis.

Keywords: Acute coronary syndrome, Cardiovascular disease, PCSK9 inhibitors

Introduction

Cardiovascular disease (CVD) is currently the leading cause of death worldwide based on data from the World Health Organization.[1,2] Acute coronary syndrome (ACS) is the most serious and life-threatening manifestation of coronary hemodialysis. Extensive evidence supports the efficacy of lipid-lowering therapy in mitigating cardiovascular events resulting from ACS.[3,4] Currently, the management and intervention for patients with ACS are crucial and challenging aspects of clinical research. The implementation of effective clinical interventions can significantly reduce the occurrence of adverse cardiovascular events in these patients.[5–7]

Novel drugs known as proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors have emerged in the field of lipid-lowering therapy. The aforementioned drugs have gained popularity in clinical practice because of their remarkable efficacy in reducing low-density lipoprotein cholesterol (LDL-C).[8–10] Although statins are considered the most effective medications for preventing cardiovascular events, they may be associated with adverse effects and not fully address the residual risk of cardiovascular events in certain patients. Consequently, alternative treatment options are required to meet the specific needs of the patients mentioned previously.[11–13] Clinical research has provided evidence that certain patients with a high risk of CVD continue to face an elevated risk even after receiving the maximum dosage of statins. The findings underscore the need for additional interventions and treatment strategies to address persistent cardiovascular risks in such individuals.[14,15] Research has also indicated that regardless of the background of statin therapy, the use of PCSK9 inhibitors can reduce the relative risk (RR) of major adverse cardiovascular events (MACEs) following ACS.[16] The introduction of PCSK9 inhibitors has revolutionized lipid-lowering therapy in clinical practice, providing clinicians with a fresh perspective. The PCSK9 inhibitors not only help maintain lower levels of LDL-C but also demonstrate the potential to significantly reduce the incidence of cardiovascular adverse events.[17–19]

We conducted a meta-analysis using published trials to investigate the effectiveness of PCSK9 inhibitors in patients who experienced ACS.

GZ and SC contributed equally to this article.

All data generated or analyzed during this study are included in this published article.

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Methods

The systematic review and meta-analysis were registered on PROSPERO (International Prospective Register of Systematic Reviews; registration no. CRD42023446871). Moreover, this study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search strategy and selection criteria

The investigations were performed before January 2023, and the articles were limited to those written in English without any restrictions. We searched the keywords "PCSK9 Inhibitors or PCSK9 Inhibitors, Cardiovascular or Cardiovascular PCSK9 Inhibitors or Inhibitors, Cardiovascular PCSK9 or PCSK9 Inhibitors Cardiovascular or Cardiovascular, PCSK9 Inhibitors" and "acute coronary syndrome or Acute Coronary Syndromes or Coronary Syndrome or Acute Coronary Syndromes or Acute Syndrome or Acute Coronary Syndromes or Acute Coronary or myocardial infarction" through PubMed, EMBASE, and the Cochrane Library. The inclusion criteria were as follows: (1) clinical studies and comparative studies: randomized controlled trials (RCTs) or non-RCTs published in English; (2) studies reporting primary or secondary outcomes; and (3) sufficient study samples and reasonable experimental design. After screening the titles and abstracts, relevant literature was downloaded for full-text reading and further screening.

Selection criteria and exclusion criteria

The included studies must satisfy the following criteria: (1) the study type was an RCT or retrospective study; (2) patients with ACS were receiving PCSK9 inhibitors; (3) the tracking time was not less than 2 months; and (4) the main outcomes were MACEs, nonfatal myocardial infarction, cardiovascular death, stroke, hospitalization for recurrent ACS, and coronary revascularization.

The exclusion criteria were as follows: (1) no consistent outcome information could be extracted from the study; (2) the studies in the literature were repeated or secondary analyses; (3) the content of the literature was the research design; and (4) the studies are meta-analysis, reviews, and animal experiments.

Data extraction and quality assessment

Two researchers independently conducted literature screening and data extraction. The information extracted in this meta-analysis encompassed fundamental details from the 5 trials, such as patient-related basic information, clinical study registration numbers, and clinical outcome measures. The Cochrane risk-of-bias or Newcastle-Ottawa Scale assessment tools were used to evaluate the quality of the included studies.

Statistical analysis

All studies were analyzed using Stata 25.0 (StataCorp, College Station, TX) and RevMan 5.4 (London, Britain). The potential publication bias was assessed using an inverted funnel plot. The results of the included studies were derived from fixed- or random-effects models when substantial heterogeneity between the estimates was observed. The effect model was determined based on the level of heterogeneity, with a fixed-effects model utilized for $I^2 < 50\%$ and a random-effects model used for $I^2 \geq 50\%$. The values of the odds ratio (OR), along with their corresponding 95% confidence interval (CI), are reported. Statistical significance was defined as $P < 0.05$.

Results

Study characteristics

Literature retrieval and screening are displayed in Fig. 1. A total of 1686 articles were retrieved, 511 duplicate documents were identified, and 1159 articles were from nonclinical studies, reviews, review guidelines, and no target data. After screening titles and abstracts, 16 articles were included for full-text evaluation. Among them, 1 study was excluded because of lack of a control group, 1 because of small sample size, 4 because of secondary analysis, 3 because of lack of target outcomes, and 2 studies because of the study design. Finally, 5 studies were included in the meta-analysis. The baseline characteristics of this study are summarized in Table 1. Overall, the aforementioned 5 studies included 38,005 patients, and the baseline characteristics (such as the type and average age of patients in each study) did not differ significantly between the 2 groups. The mean follow-up time was 3.0 to 33.6 months.

Risk of bias

The risk of bias for all included trials is presented in Fig. 2 and Fig. 3 and Table 2. All included studies were assessed using the Cochrane bias risk or Newcastle-Ottawa-Scale. Two researchers independently assessed the hidden bias risks of random sequence generation and allocation

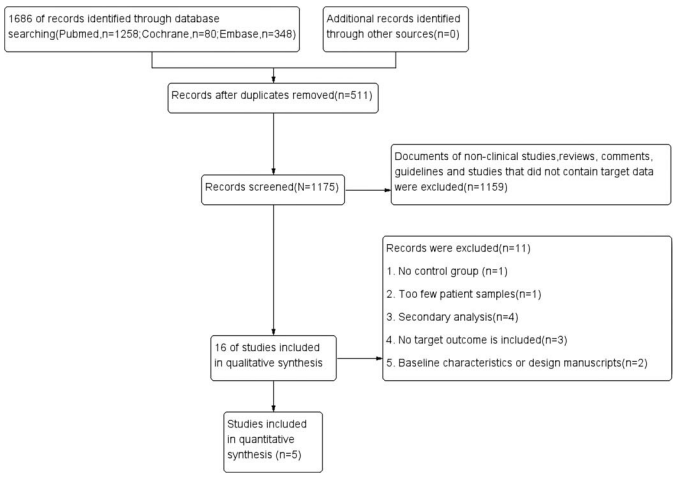

Figure 1. Flow-process diagram of the literature search.

Table 1

Characteristics of the Included Studies

Study	Year	Country	Patients	T/N	Age (T/N Mean ± SD), y	Drugs (T/N)	Follow-up, mo	Outcomes*	Clinical Trial Registration No.	Type of Study
Furtado et al.[30]	2017	49 Countries	Patients with prior ACS	8510/8563	62.5 ± 9.1/ 62.5 ± 8.9	Evolocumab/matching placebo	26.40	I, II, III, IV, VI	NCT01764633	RCT
Konstantinos et al.[31]	2019	Switzerland	ACS	155/153	60.5 ± 12.0/ 61.0 ± 10.7	Evolocumab/matching placebo	2.00	I, II, III, IV, V, VI	NCT03287609	RCT
Schwartz et al.[32]	2018	57 Countries	ACS	9462/9462	58.5 ± 9.3/ 58.6 ± 9.4	Alirocumab/matching placebo	33.60	I, II, III, IV, V, VI	NCT01663402	RCT
Yan et al.[33]	2022	China	Extremely high-risk ACS	68/68	62.2 ± 12.3/ 62.2 ± 11.4	Evolocumab/matching placebo	3.00	I, II, III, IV, V,	Unclear	RCT
Zhang et al.[34]	2022	China	ACS	414/1150	62.1 ± 10.9/ 62.2 ± 10.0	Evolocumab/matching placebo	18.00	I, II, III, IV, V, VI	ChiCTR2100049364	Retrospective

ACS, acute coronary syndrome; MACEs, major adverse cardiovascular events; RCT, randomized controlled trial; T/N, treatment group/nontreatment group.

*I: MACEs; II: nonfatal myocardial infarction; III: cardiovascular death; IV: stroke; V: hospitalization for recurrent ACS; VI: coronary revascularization.

(selection bias), blindness of participants and personnel (performance bias), blindness of outcome evaluation (test bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. The results of the evaluation demonstrated that all 6 studies had a low risk of bias, and all trials were considered to have low attrition and reporting bias based on a review of their programs on ClinicalTrials.gov and the results in publications.

Primary outcomes

Five studies (4233 cases) reported a statistically significant reduction in the incidence of MACE in patients with ACS treated with PCSK9 inhibitors. Moreover, in the 5 studies, statistical heterogeneity was observed ($P = 0.13$, $I^2 = 44\%$). A fixed-effects model combined with effect size was used for the analysis. Data confirmed that the incidences of MACE were 10.19% and 12.05% in the treatment and placebo groups, respectively. Results established that PCSK9 inhibitors reduced the incidence of MACE (OR: 0.83; 95% CI: 0.77–0.88; $P < 0.00001$) (Fig. 4A). The differences between the 2 groups were statistically significant.

Five studies (2260 cases) reported a statistically significant reduction in the incidence of nonfatal myocardial infarction in patients with ACS treated with PCSK9 inhibitors, and statistical heterogeneity was observed ($P = 0.06$, $I^2 = 56\%$). A random-effects model combined with effect size was used for the analysis. The data demonstrated that the incidence of nonfatal myocardial infarction was 5.28% in the treatment group and 6.60% in the placebo group. Results confirmed that PCSK9 inhibitors reduced the incidence of nonfatal myocardial infarction (RR: 0.80; 95% CI: 0.74–0.87; $P < 0.00001$) (Fig. 4B). The differences between the 2 groups were statistically significant.

Five studies (796 cases) reported a significant reduction in the incidence of cardiovascular death in patients with ACS treated with PCSK9 inhibitors, and statistical heterogeneity was observed ($P = 0.27$, $I^2 = 23\%$). A fixed-effects model combined with effect size was used for the analysis. Data demonstrated that the incidence of cardiovascular death was 2.06% and 2.13% in the treatment and placebo groups, respectively. Moreover, results exhibited that PCSK9 inhibitors reduced the incidence of cardiovascular death (OR: 0.96; 95% CI: 0.83–1.10; $P = 0.56$) (Fig. 4C). No statistically significant differences in outcomes were identified between the 2 groups.

Five studies (540 cases) reported a statistically significant reduction in the incidence of stroke in ACS patients treated with PCSK9 inhibitors, and statistical heterogeneity was observed ($P = 0.64$, $I^2 = 0\%$). A fixed-effects model combined with effect size was used for the analysis. Data established that the incidences of stroke were 1.21% and 1.62% in the treatment and placebo groups, respectively. Furthermore, results displayed that PCSK9 inhibitors reduced the incidence of stroke (OR: 0.74; 95% CI: 0.63–0.88; $P = 0.007$) (Fig. 4D). The differences between the 2 groups were statistically significant.

Four studies (130 cases) reported a significant reduction in the incidence of hospitalization for recurrent ACS in patients treated with PCSK9 inhibitors, and statistical heterogeneity was observed ($P = 0.55$, $I^2 = 0\%$). A fixed-effects model combined with effect size was used for the analysis. Data demonstrated that the incidences of hospitalization for recurrent ACS were 0.44% and 0.80% in the treatment and placebo groups, respectively. Results also confirmed that PCSK9 inhibitors reduced the incidence of hospitalization for recurrent ACS (OR: 0.57; 95% CI: 0.40–0.83; $P = 0.003$) (Fig. 4E). The differences between the 2 groups were statistically significant.

Four studies (3153 cases) reported a statistically significant reduction in the incidence of coronary revascularization in patients with ACS treated with PCSK9 inhibitors, and statistical heterogeneity was observed ($P = 0.31$, $I^2 = 17\%$). A fixed-effects model combined with effect size was used for the analysis, and the data determined that the incidences of coronary revascularization were 7.56% and 9.06% in the treatment and placebo groups, respectively. Results demonstrated that PCSK9 inhibitors reduced the incidence of coronary revascularization (OR: 0.82; 95% CI: 0.76–0.88; $P < 0.00001$) (Fig. 4F). The differences between the 2 groups were statistically significant.

The funnel plots demonstrated symmetrical distributions of the effect size of nonfatal myocardial infarction, cardiovascular death, stroke, hospitalization for recurrent ACS, and coronary revascularization on either side of the pooled estimate but a nonsymmetrical distribution of the effect size of MACE (Fig. 5).

Discussion

Our meta-analysis revealed that the administration of PCSK9 inhibitors to patients with ACS resulted in a significant improvement in

Table 2

Quality assessment of 1 retrospective study by using Newcastle-Ottawa-Scale quality evaluation tool.

Author	Year	Selection	Comparability	Exposure	Study design	Total points
Zhang et al.[34]	Zhang	***	*	**	Retrospective	6

* represents 1 point.

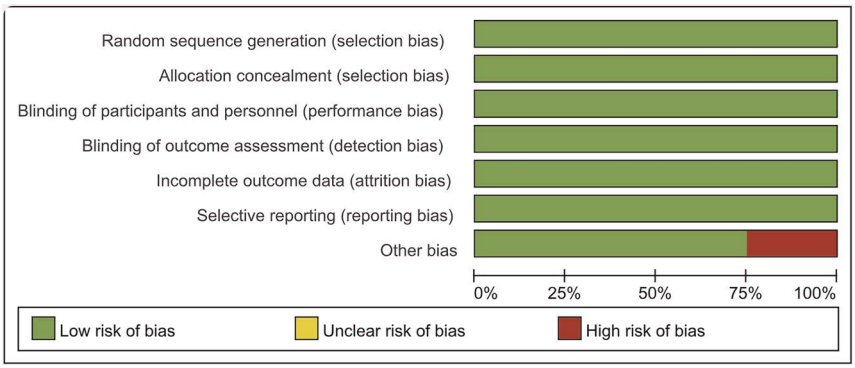

Figure 2. Risk-of-bias graph: the distribution of methodological quality of involved studies.

prognosis compared with the placebo group. Improvements were primarily observed in the reduction of MACE, nonfatal myocardial infarction, cardiovascular death, stroke events, hospitalization for recurrent ACS, and the need for coronary revascularization.

In recent years, a growing interest in the extrahepatic functions of PCSK9, including the direct impact of PCSK9 on atherosclerotic plaques, can be observed.[20] Liu et al.[21] discovered that PCSK9 inhibitors exhibited effects comparable to those of placebo. No statistically significant differences were observed in terms of single-dose pharmacokinetic and pharmacodynamic parameters, safety, or tolerability. The results of 3 cardiovascular outcome trials by Sabatine[10] demonstrated that PCSK9 inhibitors significantly decreased the risk of major vascular events. Importantly, the positive effects were not accompanied by any significant adverse events, such as excessive myalgia, elevated plasma liver transaminase levels, diabetes, or neurocognitive complications.[22] Cordero et al.[23] conducted comprehensive data analysis and demonstrated that the use of PCSK9 inhibitors resulted in a 19% reduction in the incidence of myocardial infarction and a 25% decrease in the occurrence of stroke. Our meta-analysis also indicated that PCSK9 inhibitors significantly reduced the occurrence of MACE.

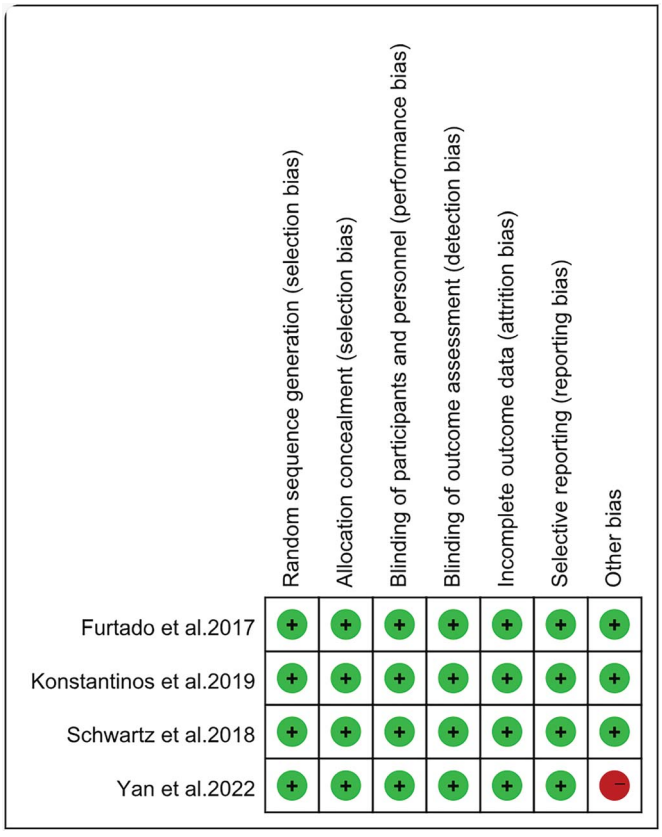

Figure 3. Risk-of-bias summary: methodological quality of involved studies. + means low risk; ? means unclear risk; – means high risk.

Previous mechanisms and epidemiological studies have provided evidence that PCSK9 proteins in the human body contribute to the increased vulnerability of coronary plaques through various pathways. These pathways include the proinflammatory oxidation of LDL-C and the direct modification of plaque composition.[24–26] The most recent guidelines also recommend considering the use of PCSK9 inhibitors in the early stages of treatment of patients who have recently experienced myocardial infarction. This approach aims to lower LDL-C levels and potentially reduce the associated morbidity. However, to establish the effectiveness and safety of this approach, conducting RCTs with a higher level of certainty are important. This provides definitive evidence regarding the benefits and risks of using PCSK9 inhibitors in such patients.[27–29] Our meta-analysis reviewed and synthesized data from multiple studies to quantify the impact of PCSK9 inhibitors on the morbidity of patients with ACS. The results of this analysis strongly support the notion that the use of PCSK9 inhibitors following ACS significantly improves clinical outcomes. Specifically, PCSK9 reduced the occurrence of MACE, nonfatal myocardial infarction, cardiovascular death, stroke, hospitalization for recurrent ACS, and the need for coronary revascularization.

In conclusion, although progress in the treatment of CVDs has been observed, the introduction of PCSK9 inhibitors provides a promising strategy for patients. The inhibitors have demonstrated significant benefits in reducing clinical complications and improving the quality of life of patients with CVDs. The safe and effective use of PCSK9 inhibitors holds great potential as a powerful therapeutic approach for the treatment of CVDs, benefiting an increasing number of patients.

Limitations

However, it is important to note that the studies in this analysis were conducted in specific populations. Therefore, the generalizability of these findings to the broader population may be limited. In summary, the application of PCSK9 inhibitors in patients with ACS has demonstrated a reduction in the probability of various

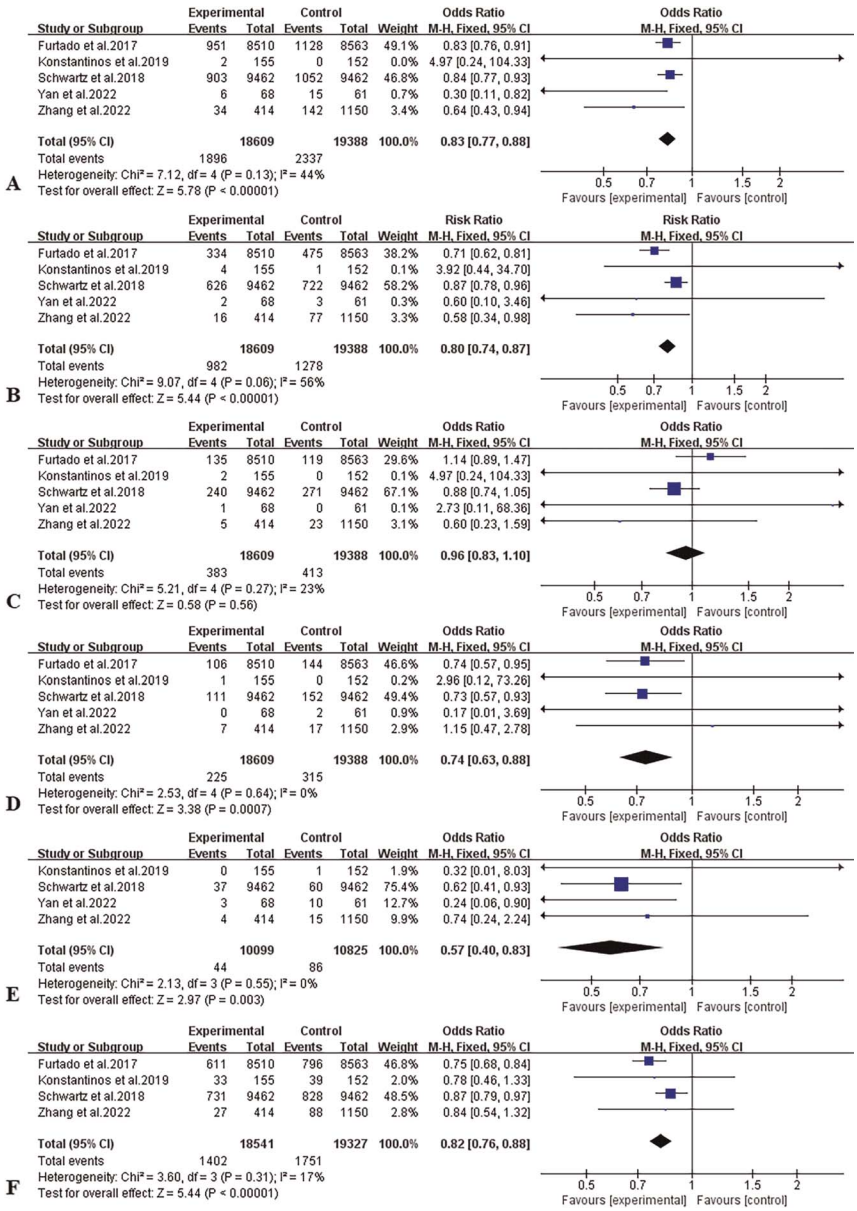

Figure 4. Forest plots depict outcomes in patients treated with PCSK9 inhibitors versus those treated with a placebo. (A–F) Forest plots depicting the comparison of PCSK9 inhibitors and placebo on MACE, nonfatal myocardial infarction, cardiovascular death, stroke, hospitalization for recurrent ACS, and coronary revascularization, respectively. Heterogeneity analysis is carried out using the Q test and among the study's variation (I^2 index). Weights are calculated from binary random-effects model analysis. ACS, acute coronary syndrome; CI, confidence interval; MACE, major adverse cardiovascular event; PCSK9, proprotein convertase subtilisin/kexin type 9.

cardiovascular events and an improvement in patient prognosis. However, owing to the limited number of included studies and patients, the potential for research bias and imprecise risk assessment exists. Therefore, further research is required to provide substantial evidence and support.

Conclusion

In summary, the application of PCSK9 inhibitors in patients with ACS has demonstrated a reduction in the probability of various cardiovascular events and an improvement in patient prognosis. However, owing to the limited number of included studies and patients, potential for research bias and imprecise risk assessment exists. Therefore, further research is required to provide substantial evidence and support.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Li B participated in the research design; Zhang G and Chang S participated in the writing of the paper; Zhao F participated in the performance of the research; Guan X and Nie Z contributed new reagents or analytical tools; Liu W participated in data analysis.

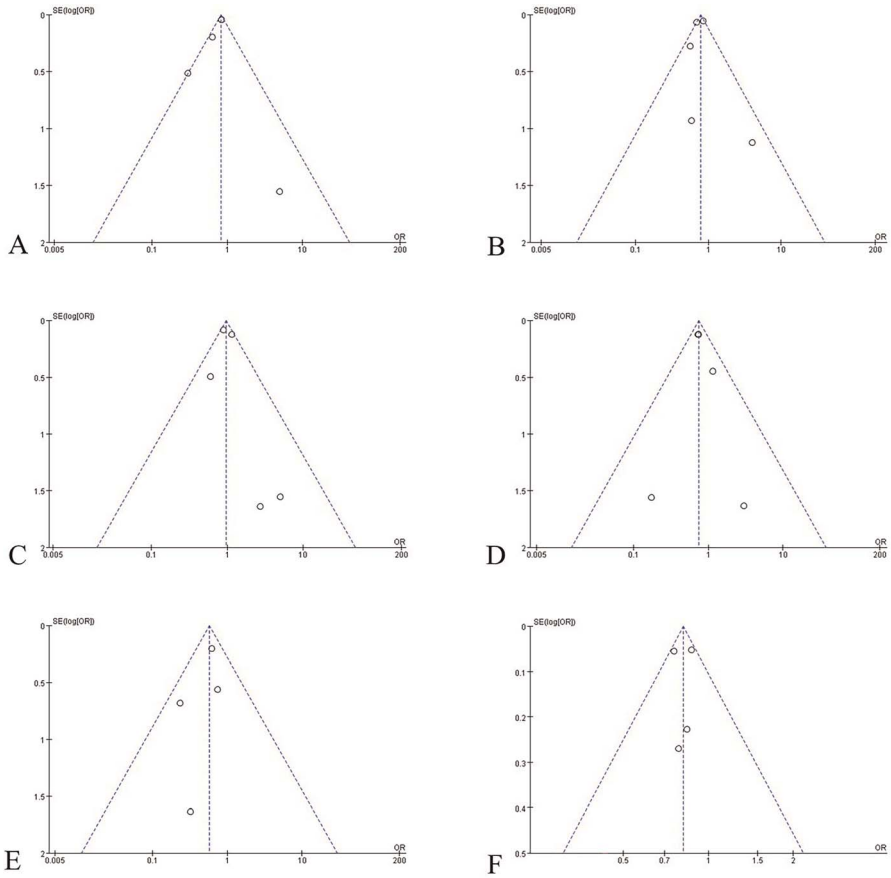

Figure 5. Funnel plots of the comparisons of MACE, nonfatal myocardial infarction, cardiovascular death, stroke, hospitalization for recurrent ACS, and coronary revascularization between PCSK9 inhibitors and placebo, respectively. (A–F) Funnel plots are used to describe the distribution of the effect size of MACE, nonfatal myocardial infarction, cardiovascular death, stroke, hospitalization for recurrent ACS, and coronary revascularization. ACS, acute coronary syndrome; MACE, major adverse cardiovascular events; PCSK9, proprotein convertase subtilisin/kexin type 9.

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Ethical approval of studies and informed consent

All studies included in this study followed the principles of the Declaration of Helsinki as revised in 2013.

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References

[1] Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol*. 2019;16(4):203–212. doi:10.1038/s41569-018-0119-4

[2] Townsend N, Kazakiewicz D, Lucy Wright F, et al. Epidemiology of cardiovascular disease in Europe. *Nat Rev Cardiol*. 2022;19(2):133–143. doi:10.1038/s41569-021-00607-3

[3] Wang L, Jin Y. Noncoding RNAs as biomarkers for acute coronary syndrome. *Biomed Res Int*. 2020;2020:3298696. doi:10.1155/2020/3298696

[4] Banach M, Penson PE, Vrablik M, et al. Optimal use of lipid-lowering therapy after acute coronary syndromes: a position paper endorsed by the International Lipid Expert Panel (ILEP). *Pharmacol Res*. 2021;166:105499. doi:10.1016/j.phrs.2021.105499

[5] Boudoulas KD, Triposciadis F, Geleris P, Boudoulas H. Coronary atherosclerosis: pathophysiologic basis for diagnosis and management. *Prog Cardiovasc Dis*. 2016;58(6):676–692. doi:10.1016/j.pcad.2016.04.003

[6] Spadaccio C, Benedetto U. Coronary artery bypass grafting (CABG) vs. percutaneous coronary intervention (PCI) in the treatment of multivessel coronary disease: quo vadis? A review of the evidences on coronary artery disease. *Ann Cardiothorac Surg*. 2018;7(4):506–515. doi:10.21037/acs.2018.05.17

[7] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;139(25):e1082–e1143. doi:10.1161/CIR.0000000000000625

[8] Gallego-Colon E, Daum A, Yosefy C. Statins and PCSK9 inhibitors: a new lipid-lowering therapy. *Eur J Pharmacol*. 2020;878:173114. doi:10.1016/j.ejphar.2020.173114

[9] Ragusa R, Basta G, Neglia D, de Caterina R, del Turco S, Caselli C. PCSK9 and atherosclerosis: looking beyond LDL regulation. *Eur J Clin Invest*. 2021;51(4):e13459. doi:10.1111/eci.13459

[10] Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. *Nat Rev Cardiol*. 2019;16(3):155–165. doi:10.1038/s41569-018-0107-8

[11] Šimić I, Reiner Ž. Adverse effects of statins—myths and reality. *Curr Pharm Des*. 2015;21(9):1220–1226. doi:10.2174/1381612820666141013134447

[12] Cai T, Abel L, Langford O, et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. *BMJ*. 2021;374:n1537. doi:10.1136/bmj.n1537

[13] Toth PP, Banach M. Statins: then and now. *Methodist deBakey Cardiovasc J*. 2019;15(1):23–31. doi:10.14797/mdcj-15-1-23

[14] Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US preventive services task force. *JAMA*. 2016;316(19):2008–2024. doi:10.1001/jama.2015.15629
[15] Bytyçi I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis. *Eur Heart J*. 2022;43(34):3213–3223. doi:10.1093/eurheartj/ehac015
[16] Diaz R, Li QH, Bhatt DL, et al. Intensity of statin treatment after acute coronary syndrome, residual risk, and its modification by alirocumab: insights from the ODYSSEY OUTCOMES trial. *Eur J Prev Cardiol*. 2021;28(1):33–43. doi:10.1177/2047487320941987
[17] Ali AH, Younis N, Abdallah R, et al. Lipid-lowering therapies for atherosclerosis: statins, fibrates, ezetimibe and PCSK9 monoclonal antibodies. *Curr Med Chem*. 2021;28(36):7427–7445. doi:10.2174/0929867328666210222092628
[18] Guo YL, Zhang W, Li JJ. PCSK9 and lipid lowering drugs. *Clin Chim Acta*. 2014;437:66–71. doi:10.1016/j.cca.2014.07.008
[19] Steffens D, Bramlage P, Scheeff C, et al. PCSK9 inhibitors and cardiovascular outcomes. *Expert Opin Biol Ther*. 2020;20(1):35–47. doi:10.1080/14712598.2020.1677604
[20] Yurtseven E, Ural D, Baysal K, Tokgözoğlu L. An update on the role of PCSK9 in atherosclerosis. *J Atheroscler Thromb*. 2020;27(9):909–918. doi:10.5551/jat.55400
[21] Liu C, Lu H, Yuan F, et al. A phase 1, randomized, double-blind, single-dose, placebo-controlled safety, tolerability, and pharmacokinetic/pharmacodynamic study of evolocumab in healthy Chinese subjects. *Clin Pharmacol*. 2019;11:145–153. doi:10.2147/CPAA.S208033
[22] Kosmas CE, Skavdis A, Sourlas A, et al. Safety and tolerability of PCSK9 inhibitors: current insights. *Clin Pharmacol*. 2020;12:191–202. doi:10.2147/CPAA.S288831
[23] Cordero A, Rodríguez-Mañero M, Fácila L, et al. Prevention of myocardial infarction and stroke with PCSK9 inhibitors treatment: a metanalysis of recent randomized clinical trials. *J Diabetes Metab Disord*. 2020;19(2):759–765. doi:10.1007/s40200-020-00557-6
[24] Momtazi-Borojeni AA, Sabouri-Rad S, Gotto AM, et al. PCSK9 and inflammation: a review of experimental and clinical evidence. *Eur Heart J Cardiovasc Pharmacother*. 2019;5(4):237–245. doi:10.1093/ehjcvp/pvz022
[25] Nicholls SJ, Kataoka Y, Nissen SE, et al. Effect of evolocumab on coronary plaque phenotype and burden in statin-treated patients following myocardial infarction. *JACC Cardiovasc Imaging*. 2022;15(7):1308–1321. doi:10.1016/j.jcmg.2022.03.002
[26] Wu NQ, Shi HW, Li JJ. Proprotein convertase subtilisin/kexin type 9 and inflammation: an updated review. *Front Cardiovasc Med*. 2022;9:763516. doi:10.3389/fcvm.2022.763516
[27] Correction to: PCSK9 (proprotein convertase subtilisin/kexin 9) enhances platelet activation, thrombosis, and myocardial infarct expansion by binding to platelet CD36. *Circulation*. 2021;143(1):e4. doi:10.1161/CIR.0000000000000948
[28] Puteri MU, Azmi NU, Kato M, Saputri FC. PCSK9 promotes cardiovascular diseases: recent evidence about its association with platelet activation-induced myocardial infarction. *Life (Basel)*. 2022;12(2):190. doi:10.3390/life12020190
[29] Laugsand LE, Åsvold BO, Vatten LJ, et al. Circulating PCSK9 and risk of myocardial infarction: the HUNT study in Norway. *JACC Basic Transl Sci*. 2016;1(7):568–575. doi:10.1016/j.jacbts.2016.06.007
[30] Furtado RHM, Fagundes AA Jr, Oyama K, et al. Effect of Evolocumab in Patients With Prior Percutaneous Coronary Intervention. *Circ Cardiovasc Interv*. 2022;15(3):e011382. doi:10.1161/CIRCINTERVENTIONS.121.011382
[31] Koskinas KC, Windecker S, Pedrazzini G, et al. Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS). *J Am Coll Cardiol*. 2019;74(20):2452–2462. doi:10.1016/j.jacc.2019.08.010
[32] Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018;379(22):2097–2107. doi:10.1056/NEJMoa1801174
[33] Hao Y, Yang YL, Wang YC, Li J. Effect of the Early Application of Evolocumab on Blood Lipid Profile and Cardiovascular Prognosis in Patients with Extremely High-Risk Acute Coronary Syndrome. *Int Heart J*. 2012;63(4):669–677. doi:10.1536/ihj.22-052
[34] Zhang Y, Zhang Y, Zhang B, et al. Early Initiation of Evolocumab Treatment in Chinese Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *Clin Ther*. 2022;44(6):901–912. doi:10.1016/j.clinthera.2022.04.010

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