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Early administration of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in patients with acute coronary syndrome: a systematic review and meta-analysis

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Abstract

Background High-intensity statin therapy is currently recommended initial guideline therapy in ACS treatment. However, only a minority of patients are achieving LDL-C attainment goal at 6 months. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are on recommended guideline therapy post-ACS if LDL-C goal attainment is not achieved after high-intensity statin (4–6 weeks) and after the addition of ezetimibe if guideline goal attainment is not achieved after an additional 4–6 weeks. Thus, it has been recommended that PCSK9 inhibitors be considered earlier post-ACS. However, the efficacy of early PCSK9 inhibitors initiation in ACS patients remains uncertain.

Methods This systematic review and meta-analysis was conducted following PRISMA guidelines. Randomized controlled trials (RCTs) and observational studies involving ACS patients who received PCSK9 inhibitors within 48 h of hospitalization were included. Common and random effects models were used to evaluate the pooled effect of early PCSK9 inhibitor administration. Nine RCTs and three cohort studies were included.

Results Early PCSK9 inhibitor administration reduced the incidence of MI, ACS hospitalization, and revascularization at 6–18 months post-ACS. Although there was a drift towards reduced stroke, all-cause mortality, and cardiovascular death, no statistically significant reduction was observed. Additionally, PCSK9 inhibitors significantly enhanced lipid control at 4–12 weeks after index hospitalization.

Conclusion Early PCSK9 inhibitors initiation in ACS patients reduces MACE and improves lipid profiles. While the results propose promising benefits in terms of stroke and mortality, further research with longer follow-up is required for more decisive evidence.

Keywords Acute coronary syndrome, PCSK9 inhibitors, Lipid lowering, MACE

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Introduction

Acute coronary syndrome (ACS) is a high-risk medical condition that requires rapid and effective treatment to prevent potential complications and reduce mortality rates [1]. Early initiation of intensive lipid-lowering treatment with greater LDL-C lowering is recommended in ACS patients to diminish the risk of additional complications [2–4].

This has long included high-intensity statin therapy, but several additional classes of lipid-lowering agents are also available to provide additional LDL-C lowering or as alternatives for individuals unable to take statins [5]. This includes proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

While chronic use of PCSK9 inhibitors in individuals with stable IHD is well-known to improve outcomes [6], whether early initiation of these agents (in the setting of ACS) might also reduce early events is less clear [7]. We aimed to address this area of uncertainty with a systematic review and meta-analysis of randomized controlled trials (RCTs) and cohort studies testing the efficacy of early administration *of* the PCSK9 inhibitors evolocumab and alirocumab, in patients hospitalized with ACS.

Methods

This systematic review and meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [8] and the study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) – PROSPERO ID: CRD42023443823 [9, 10].

Criteria for Considering Studies for this Review.

Types of studies

Randomized Controlled Trials (RCTs) and observational studies including adult patients with a diagnosis of ACS reporting head-to-head comparison of PCSK9 inhibitors started in the first 48 h after presentation to the hospital (early administration strategy) to usual care were included. Case reports, review articles, trial design protocols, non-comparative studies, and conference abstracts were dismissed.

Participants and interventions

Patient exclusion criteria differed across studies but generally included known allergies to PCSK9 inhibitors, conditions likely to change the clinical course independent of ACS, or conditions that could jeopardize their safety or limit their participation in the respective trial.

Outcome measures

Primary outcomes of the study included major adverse clinical events (MACE), including mortality (all-cause or cardiovascular), stroke, non-fatal MI, ACS hospitalization, and need for revascularization at 24 to 72 weeks post-index hospitalization. Secondary outcomes included laboratory measurements of lipid profile including apolipoprotein B (Apo B), apolipoprotein A-I (Apo A), lipoprotein(a) (Lp(a)), total cholesterol, *high-density* lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and triglycerides (TG) at 4–12 weeks post-index hospitalization.

Search strategy

After identifying relevant keywords and search terms (Supplementary Material), we performed a systematic search of the following electronic databases: PubMed, EMBASE, Cochrane Library, Clinicaltrials.gov, and WHO's International Clinical Trials Registry Platform, from January 1, 2014, until July 11, 2023. Only English language studies were included. Reference lists of eligible studies and relevant reviews on the topic were also screened.

Data collection and management

The process involved importing the findings of the systematic search into Endnote software version 20.0 (from Clarivate PLC in London, United Kingdom). Two independent authors, SM and AN, reviewed study titles and abstracts, and any discrepancies were addressed by a third reviewer, HS. The selected studies were then retrieved in full, and data was extracted using a pre-designed form which included: name of the first author, study location, study type, sample size for each comparison group, baseline characteristics, laboratory markers, and the presence/absence of clinical events.

Risk of bias assessment

The quality of RCTs included in the study was assessed using version 2.0 of the Cochrane Risk of Bias Assessment Tool for Randomized Trials (RoB2) [10, 11]. The Newcastle-Ottawa Scale (NOS) [12] was used to assess the quality of nonrandomized studies included in our meta-analyses. Selection, comparability, and ascertainment of exposure/outcome were assessed in each nonrandomized study. Two authors (SM, AN) assigned stars in each category, and conflicts were resolved through consensus.

Data analysis and investigation of heterogeneity

All statistical analyses were conducted using R Programming language (R for Windows, version 4.1.3, Vienna, Austria) and R Studio version 1.1.463 (Posit PBC, Boston, MA, United States) utilizing the "tidyverse" and "meta" statistical packages. Risk ratios with 95% confidence intervals were calculated for binary variables, while mean and standard deviation (SD) were calculated for continuous variables, to compare treatment methods

mean difference (MD) was calculated. In studies that reported median and interquartile (IQR) ranges, we used the method developed by Lou et al. [13] and Wan et al. [14] to calculate means and standard deviations. Heterogeneity was assessed using the I^2 statistic, with significant heterogeneity defined as $I^2 > 70\%$. If heterogeneity was significant, we used a random effects model to estimate the effect size of the pooled data; otherwise, a fixed effects model was used. Sensitivity and subgroup analyses were conducted to identify sources of heterogeneity when possible. Funnel plots were not produced for this study as the number of included papers was less than 10.

Sensitivity analysis

We performed a leave-one-out sensitivity analysis to evaluate the robustness of our meta-analysis for the LDL-C outcome by iteratively removing one study at a time and recalculating the pooled estimate.

Results

Study selection

Figure 1 depicts the selection process for the study. The database search produced 1301 records in total. 1054 items were retrieved for preliminary screening after duplicates were removed. Under the guidance of a senior team member, two independent reviewers examined the entirety of 102 articles before determining their ultimate eligibility. Publications that did not include randomized clinical trials and cohort studies were disregarded (Fig. 1). Finally, nine randomized clinical trials comprising a total of 1268 participants and three cohort studies including 1982 participants, were included in this analysis (Table 1).

Characteristics of included studies

All 12 studies included in our analyses were published between 2019 and 2023. The mean±SD age range was similar in both RCTs and cohort studies and the majority of patients were male (Table 1). Seven RCTs and one cohort study enrolled patients with both non-ST-elevation (NSTE) ACS and ST Elevation Myocardial Infarction (STEMI) [15–22], one RCT and one cohort included only patients with STEMI [23, 24], and one RCT and one cohort study only included patients with NSTE-ACS [25, 26]. One RCT and three cohort studies reported MACE [16, 20, 23, 26] with at least 6 months of clinical
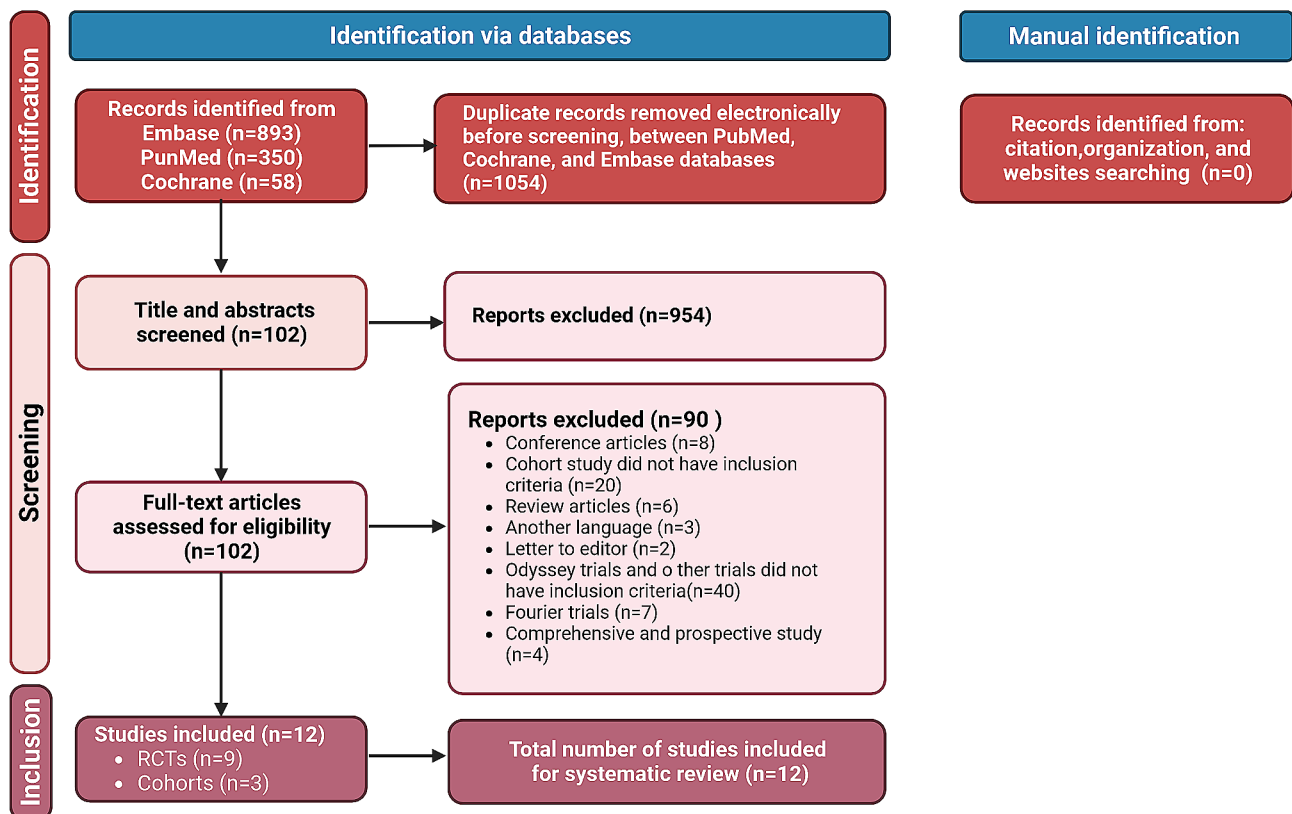
PRISMA

Fig. 1 Flowchart of the study selection process. RCT, randomized controlled trial

Table 1 Characteristic and demographic information of included studies

First Author and Year	Study Region	Study Type	Number of patients		Age (MEAN±SD)		Male Sex %		Study design	Outcomes
Koskinas 2019 [18]	Switzerland	RCT (EVO-PACS trial)	155	153	60.5±12	61±10.7	82	80.39	• Administration of 420 mg Evolocumab in patients with non-STE-MI less than the first 24 h and in patients with STE-MI less than the first 72 h. • Follow-up time was determined for 8 weeks.	• Mean LDL-C levels decreased from 3.61 mmol/L to 0.79 mmol/L during 8 weeks of follow-up in the group treated with 420 mg Evolocumab every 4 weeks and it changed from 3.42mmol/L to 2.06 mmol/L in the placebo group. 95.7% of patients in the Evolocumab group and 37.6% of patients in the placebo group had LDL-C levels less than 1.8 mmol/L after8 weeks. Other atherogenic lipid particles were significantly reduced in the Evolocumab group compared to the placebo. • Serious adverse events occurred in 7.7% of patients in the Evolocumab group and in 7.2% of patients in the Placebo. All-cause death included 2 patients in the Evolocumab group and no patients in the placebo. • Mean levels of CRP changes during follow-up did not have significant differences between groups.
Leucker 2020 [25]	US	RCT (EVACS trial)	30	27	55±13 (57patients)		73	40	• Administration of 420 mg Evolocumab in patients with non-STE-MI less than the first 24 h. • Follow-up time was 4 weeks after administration of the PCSK-9 inhibitors.	• Mean LDL-C level decreased from 91±35 mg/dl to 35±24 after 4 weeks in the group treated with 420 mg Evolocumab and it changed from 89.6±41 mg/dl to 64±27 in the placebo group.
Li 2021 [20]	China	RCT	54	45	60.6±10.1	58.6±10.6	62	66	• Administration of 140 mg Evolocumab every 2 weeks in patients with non-STE-MI, STE-MI, and unstable angina less than the first 72 h. • Follow-up time was 8 weeks after administration of the PCSK-9 inhibitors.	• The mean LDL-C level decreased from 124 to 44 mg/dl after 8 weeks in the group with 140 mg Evolocumab every two weeks and it changed from 104 to 81 mg/dl in the placebo group. • 96.3% of patients in the experimental group and 13.3% of patients in the placebo group had LDL-C levels less than 55 mg/dl after 8 weeks. • Reductions in VLDL-p, LDL-P, IDL-P, and ApoB levels after weeks of treatment was significantly different between groups.
Hao 2022 [19]	China	RCT	58	68	62.21±12.31	62.22±11.44	66	70.58	• Administration of 140 mg Evolocumab every 2 weeks in patients with non-STE-MI and STE-MI within 48 h after PCI. • Follow-up time was 3 months after administration of the PCSK-9 inhibitors.	• The mean LDL-C level decreased from 3.54 to 0.57 mmol/L in the patients who were treated with 140 mg Evolocumab every 2 weeks and it changed from 3.52 to 1.26 mmol/L in the control group. Evolocumab decreased the Lp (a) level, but the average level of Lp (a) in the control group increased from baseline after treatment. Additionally, when compared to the control group, evolocumab further decreased the levels of apolipoprotein B/A1, cholesterol, and apolipoprotein B. • The incidence of MACEs following PCI was lower in the evolocumab group than in the control group throughout the 3-month follow-up (8.82% versus 24.59%), and the combination of evolocumab with statins and ezetimibe did not increase the frequency of adverse responses (13.24% against 11.48%).

Table 1 (continued)

First Author and Year	Study Region	Study Type	Number of patients	Age (MEAN ± SD)	Male Sex %	Study design	Outcomes
Mehta 2022 [24]	Canada	RCT	38 30	61.37 ± 11.04 63.63 ± 10.38	71.05 93.33	• Administration of 150 mg Alirocumab every 4 weeks in the patients with STE-MI. The first dose was applied within 24 h after PCI. • Follow up time was 45 days after administration of the PCSk-9 inhibitors.	• The mean LDL-C level decreased from 2.97 mmol/L to 0.75 mmol/L in participants treated with 150 mg alirocumab every 2 weeks after 45 days follow-uo and it changed from 2.87 mmol/l to1.30 mmol/L in the control group. • One death occurred in the control group while none occurred in the alirocumab group. Neither group experienced a myocardial infarction (MI) or a stroke. In the alirocumab group, there were 4 heart failure episodes, while there were none in the control group. There were no documented allergic reactions, cerebral hemorrhages, or local injection site responses. There was just one minor bleed in the control group, with no significant bleeds.
Okada 2022 [17]	Switzerland	RCT	52 50	66.4 ± 13.1 63.4 ± 14	82.69 94	• Administration of 140 mg Evolocumab every 2 weeks in the patients with non-STE-MI and STE-MI within 24 h after PCI. • Follow up time was 4 weeks after administration of the PCSk-9 inhibitors.	• Themean Lp a level reduced from 46.7 ± 18.3 mg/dl to 40.8 ± 21.6 in the patients treated with 140 mg Evolocumab every two weeks and it increased from 43.8 ± 15.1 to 57.7 ± 18.8 in the control group after 4 weeks follow-up.
Raber 2022 [16]	Switzerland	RCT (PACHMAN)	148 152	58.4 ± 10 58.6 ± 9.4	83.78 78.28	• Administration of 150 mg Alirocumab every 2 weeks in the patients with STE-MI and non-STE-MI within 24 h after PCI. • Follow up time was 2, 4, 24, and 52 weeks after administration of the PCSK-9 inhibitors.	• The mean LDL-C level reduced from 154.8 to 23.6 mg/dL in the alirocumab group and it reduced from 150.9 to 74.4 in the placebo group after 52 weeks follow-up. • Patients taking alirocumab showed statistically insignificant differences in high-sensitivity C-reactive protein, but significantly higher reductions in triglycerides, lipoprotein (a), and apolipoprotein B. Compared to 72.8% of patients who received a placebo, adverse events occurred in 70.7% of the participants receiving alirocumab.
Va- vurana- kis 2022 [15]	US	RCT	35 39	56.9 ± 10 56.8 ± 11.5	82.85 46.15	• Administration of 420 mg Evolocumab in the patients with non-STE-MI and STE-MI within 24 h after hospitalization. • Follow up time was 30 days after administration of the PCSk-9 inhibitors.	• The level in the placebo-treated patients significantly increased from the pretreatment level, rising from 64 nmol/L to 80 nmol/L at hospital discharge and to 82 (37,265) nmol/L at 30 days. In contrast, regardless of pretreatment Lp(a) levels, there was no significant change from the pretreatment level in the patients treated with 420 mg evolocumab. • 13 patients in the Evolocumab group and 12 patients in the control group had non-serious adverse events and 7 patients in the Evolocumab group and 9 patients in the placebo grouphad a serious adverse event.

Table 1 (continued)

First Author and Year	Study Region	Study Type	Number of patients		Age (MEAN±SD)		Male Sex %		Study design	Outcomes
Yamashita 2023 [22]	Japan	RCT	62	62	66.9±10.2	66±11.6	77	77	• Administration of 140 mg Evolocumab every 2 weeks, 150 mg Alirocumab every 4 weeks, and 75 mg Alirocumab every 2 weeks in the patients with non-STE-MI, STE-MI, and unstable angina. • Follow up time was 1, 3, and 12 months after administration of the PCSK-9 inhibitors.	• At 1 and 3 months, the LDL-C levels in the group with PCSK9 antibodies were much lower than those in the group without PCSK9 antibodies, but at 1 year, they were similar and still above 70 mg/dL. At one month, HDL levels were noticeably higher in the PCSK9 antibody group than in the control group. During the monitoring period, there were no discernible differences in the triglyceride levels of the two groups. • The secondary endpoint of hospitalization for worsening heart failure did not differ across the groups. Abnormal serum CK values, myalgia frequency, or liver dysfunction did not differ significantly between the groups.
Zhang 2022 [21]	China	Cohort	414	1150	62.1±10.9	62.2±10	62.31	59.21	• Administration of 140 mg Evolocumab every 2 weeks in the patients with non-STE-MI, STE-MI, and unstable angina after PCI. • Follow up time was 18 months after administration of the PCSK-9 inhibitors.	• In comparison to statins alone, using of 140 mg Evolocumab every two weeks and statins lowered LDL-C levels from baseline values by 42.48% at 18 months. Evolocumab and statins significantly lowered the primary outcome after multivariable adjustment. Additionally, Evolocumab consistently decreased the main result in all significant subgroups. • There were no discernible differences in any adverse events for the safety outcomes between the groups.
Ji 2023 [26]	China	Cohort	55	55	60.45±11.67	61.23±10.34	69	65.45	• Administration of 140 mg Evolocumab in the patients with non-STE-MI less than the first 24 h. • Follow up time was 6 months after administration of the PCSK-9 inhibitors.	• After 6 months of treatment with 140 mg Evolocumab, the PCSK9 inhibitor group had significantly lower TG, TC, LDL-C, Lp(a), hs-CRP, TNF-, and IL-6 levels and IMR values than the control group. The PCSK9 Inhibitor group was found to experience TMPG grade much more frequently than the Control group. There were no discernible MACE or adverse reaction variations across groups.
Zhao 2023 [23]	China	Cohort	102	253	65.96±6.29	65.19±6.3	61	65	• Administration of 140 mg Evolocumab every 2 weeks in the patients with STE-MI. • Follow up time was 12 months after administration of the PCSK-9 inhibitors.	• Lesion length and diameter stenosis were considerably reduced in the statin plus Evolocumab group. While the group showed noticeably higher QFR and minimum lumen diameter (MLD) values. Plaque lesion length and statin plus Evolocumab were both independently linked to rehospitalization for unstable angina (UA) within a year. • Statin plus Evolocumab significantly decreased TC and LDL-C levels compared to statin monotherapy, despite the fact that TC, LDL-C, and CRP levels upon admission were not statistically different. • Furthermore, we discovered that while all-cause death, cardiovascular death, nonfatal AMI, or stroke did not significantly change between the two groups, the proportion of patients who required re-hospitalization and had coronary stents placed for UA decreased dramatically in the statin plus Evolocumab group.

follow-up. Table 1. **Characteristic and demographic information of included studies.**

Outcomes

Primary outcomes- clinical outcomes

In comparison to usual care, at 6–18 months post index hospitalization, early initiation of PCSK9 inhibitors in patients with ACS resulted in a lower incidence of MI, ACS hospitalization, and need for revascularization with risk ratios (RR) of 0.59 (95%CI 0.38–0.92), 0.53 (95% CI 0.34–0.83) and 0.71 (95%CI 0.50-1.00), and estimated numbers needed to treat of 35,38, and 37, respectively (Fig. 2A and B, and 2C). However, while RR for stroke (CVA) (0.94; 95%CI 0.51–1.72), all-cause mortality (0.66; 95%CI 0.31–1.40), and cardiovascular death (0.79; 95%CI 0.35–1.79), tended to be reduced with PCSK9 inhibitor use, the effects were not statistically significant at 6–18 months post-ACS (Fig. 2D and E, and 2F).

Secondary outcomes -lipid profiles

The random effect model analysis showed significant reductions in total (MD: -39.27, 95%CI (-52.08; -26.46)) and LDL-C (MD: -37.58, 95% CI (-46.63; -28.530)) in patients receiving early PCSK9 inhibitor treatment vs. control groups (Fig. 3A, B), although there was high heterogeneity.

Common effects modeling revealed a significant difference between the PCSK9 inhibitor group and the placebo group in Lp(a) levels (MD: -10.91, 95% CI (-16.47; -5.35)), and random effects modeling demonstrated a significant difference in Apo B levels between the two groups (MD: -27.03, 95% CI (-27.03; -17.76)), respectively (Fig. 3C and D). The results of HDL-C, TG, and Apo A levels during short-term follow-up (4–12 weeks) are presented in Supplementary files (Figure S1).

Sensitivity analysis

Figure S2 shows the leave-one-out sensitivity analysis for the LDL-C outcome. The point estimates and confidence intervals are consistent across the iterative removal of each study, indicating that no single study had an undue influence on the overall result and confirming the robustness of our meta-analysis for this outcome.

The methodological risk of bias

The results of quality assessments, using the Cochrane Risk of Bias 2 (RoB 2) tool for RCTs and the Newcastle Ottawa scale (NOS) for cohort studies, are represented in Figs. 4 and 5; Table 2. Except for the study by Li et al. [20]. which was found to have a high risk of bias due to the high-risk randomization process, all other included RCTs and cohorts were deemed to be of high quality.
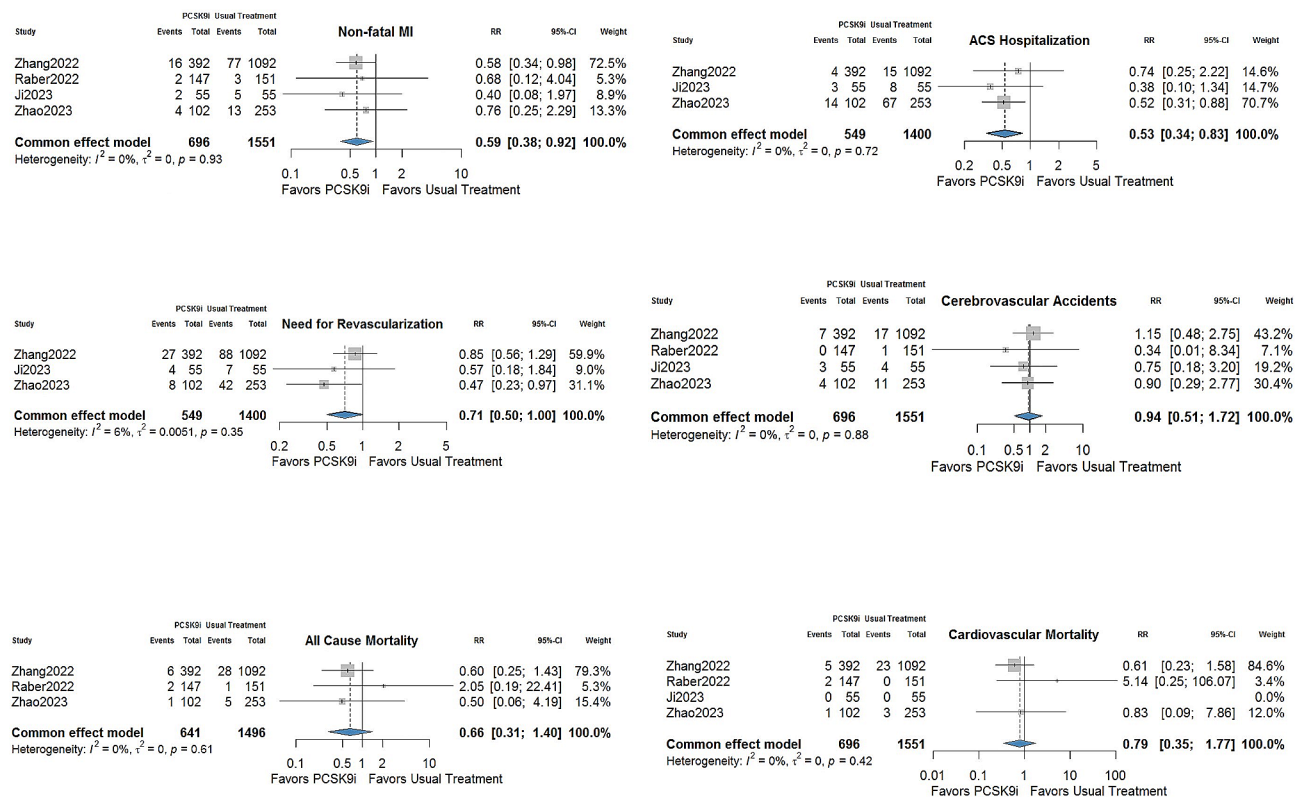

Fig. 2 (A–F) Forest plot showing the observed outcomes and the estimate of the common effect models for MI, ACS hospitalization, *Need for* Revascularization, *Cerebrovascular Accidents*, all-cause mortality, *and Cardiovascular Mortality* [16, 21, 23, 26]
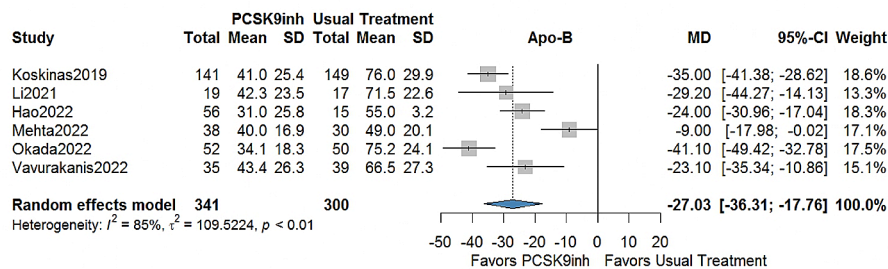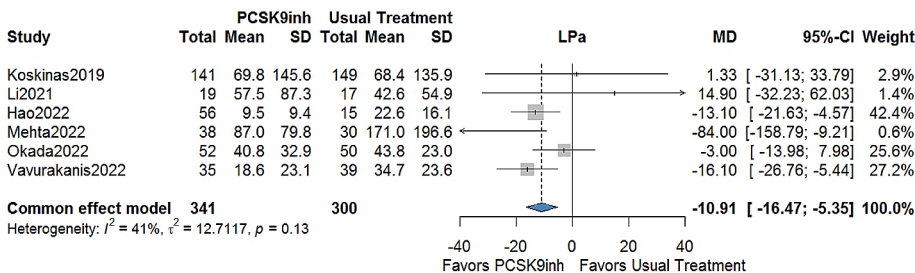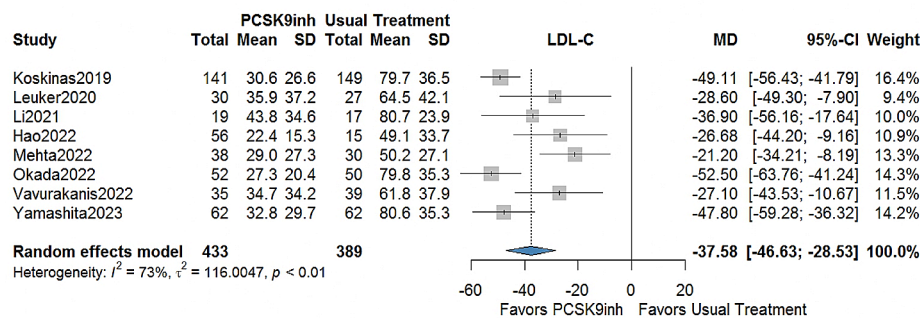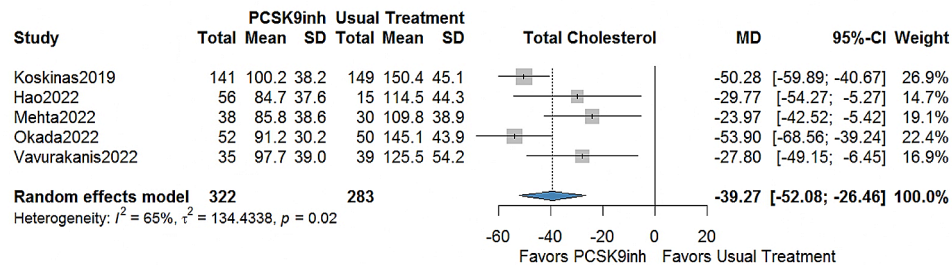
Fig. 3 (**A–D**) Forest plot showing the observed outcomes and the estimate of the common and random effect models for Total cholesterol, LDL-C, Lipoprotein a, and Apo lipoprotein B, at Short-term *Follow-up* (4–12 weeks) [15, 17–20, 22, 24, 25]
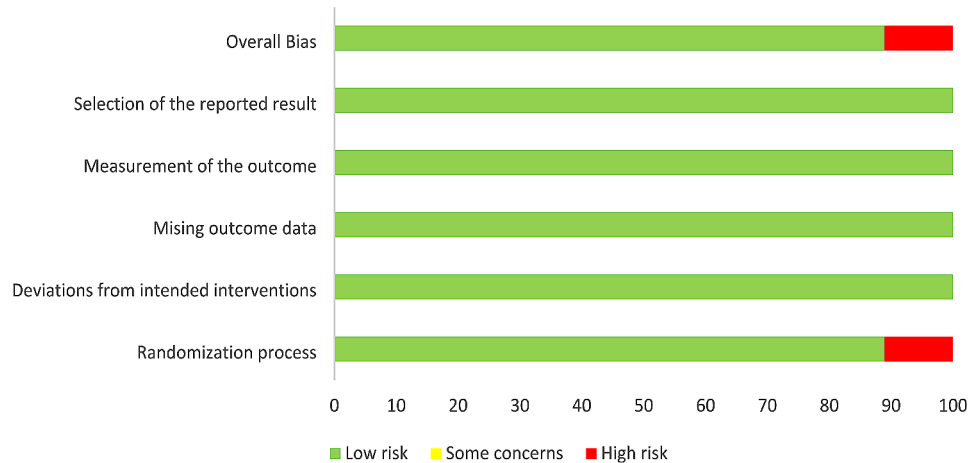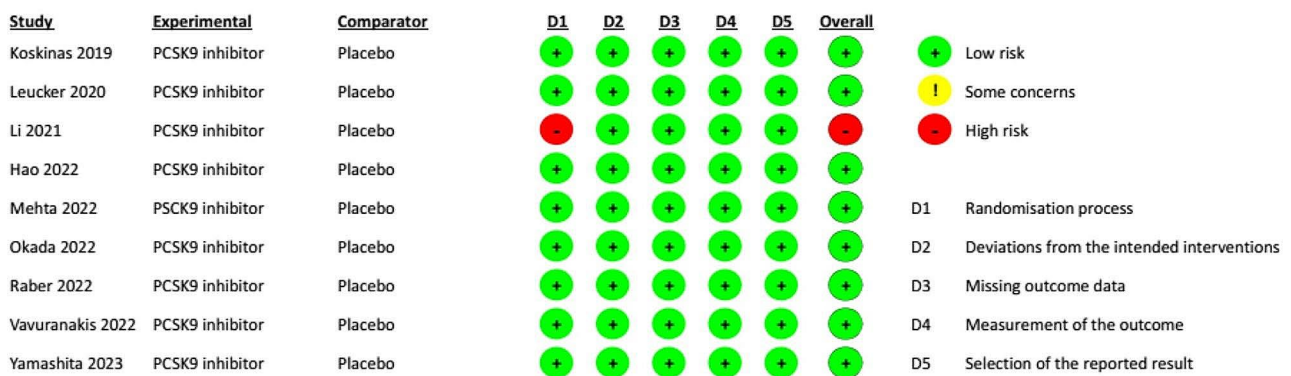
Fig. 4 Risk of bias graph in RCTs

Fig. 5 Risk of bias summary in included RCTs [15–20, 22, 24, 25]

Table 2 Quality assessment of cohort studies

First Author and Year	Selection	Comparability	Exposure/Outcome	Total Score
Zhang 2022 [26]	****	**	***	*********
Ji 2023 [9]	****	**	***	*********
Zhao 2023 [23]	****	**	***	*********

Discussion

Our pooled analyses reveal that, at 6–18 months following ACS, adverse clinical events are reduced with administration/initiation of PCSK9 inhibitors in the first 48 h after presentation to the hospital. In comparison to the control group receiving standard therapy, the PCSK9 antibody group saw decreased incidence of MI, ACS-related hospitalization, and revascularization. Early PCSK9 inhibitors therapy also suggested potential advantages in terms of CVA, cardiovascular mortality, and all-cause mortality. In addition, early implementation of PCSK9 inhibitors significantly reduced total cholesterol, LDL-C, Apo B, and Lp(a) levels within 4–12 weeks of initiation.

Our meta-analysis provides evidence supporting the use of early PCSK9 inhibitor administration in ACS patients to improve clinical outcomes and lipid profiles. Early administration of PCSK9 inhibitor therapies should be considered by physicians in patients with ACS, particularly those with high LDL-C levels or those who can't accomplish acceptable LDL-C reduction with statin therapy alone. However, treatment decisions should be modified based on medical history, risk factors, and the presence of concurrent medical conditions. Further study is needed to identify the ideal timing and duration of PCSK9 inhibitor therapies in ACS patients in order to evaluate the long-term safety and efficacy of this treatment approach. Early PCSK9 inhibitor therapy could

stabilize vulnerable plaques, reduce inflammation, and prevent recurrent cardiovascular events [27–29].

Primary outcomes- clinical outcomes

To our knowledge, no meta-analysis has been conducted so far that has evaluated the effects of early implementation of PCSK9 inhibitors in ASC patients. Our assessment of both observational studies and RCTs with a minimum follow-up duration of 6 months revealed that the prompt use of PCSK9 inhibitors in ACS patients resulted in lower rates of MI, hospitalization, and the need for revascularization at mid-term follow-up (6–18 months) in comparison to placebo or standard of care. The *biological* plausibility of these early clinical benefits *is* supported by studies showing PCSK9i in ACS patients reduces plaque burden and increases fibrous cap thickness [16, 30, 31].

While there is limited knowledge *of* early initiations of PCSK9 inhibitors in ACS management, many studies have assessed the efficacy and safety of these drugs in stable patients. Turgeon et al. [32] found that PCSK9 inhibitors lowered the risk of composite MACE by 17% in a meta-analysis encompassing 23 RCTs with *a* minimum follow-up of 6 months. The effects of PCSK9 inhibitors on all-cause and cardiovascular mortality, however, were not statistically significant. Furthermore, a recent meta-analysis assessing the efficacy of PCSK9 inhibitors on MACE in adults with atherosclerotic cardiovascular disease found that both alirocumab and evolocumab reduced MACE at a mean 1.56 years follow-up with the corresponding number needed to treat of 36. This reduction also included a decrease in CVA and coronary revascularization [33].

While our results demonstrated that early administration of PCSK9 inhibitors *shows* better effectiveness than conventional therapy in terms of CVA, cardiovascular mortality, and all-cause death, the difference was not statistically significant. There are three critical factors to consider in this situation. To begin with, it is conceivable that the period of follow-up was insufficient to appropriately assess these effects. Second, just one RCT investigated MACE outcomes for more than 6 months [16], stressing the need for further trials with longer follow-up lengths to offer greater clarification on this issue and finally the incidence of aforementioned adverse events was too low, so it might be possible that studies were not powered enough to detect a significant shift in these outcomes.

Secondary outcomes- lipid profiles

The aggressive and rapid reduction of LDL-C levels has been generally acknowledged as an important method to reduce rates of MACE in high-risk individuals [34–36]. According to previous guidelines, it was recommended to re-evaluate lipid profiles 4–6 weeks after initiation of lipid-lowering therapies in post-NSTE-ACS management [3, 37]. Additionally, as a general suggestion, 8 ± 4 weeks is an appropriate timeframe for assessing the effectiveness of lipid-lowering treatment [3]. Therefore, in this meta-analysis, we assessed lipid profiles in both treatment groups regarding lipid profile at 4–12 weeks post initial treatment.

In congruence with a previous network meta-analysis evaluating *patients* with hypercholesterolemia [38], our pooled analysis of patients with the diagnosis of ACS confirmed the superiority of early usage of PCSK9 inhibitors compared to the usual treatment group regarding LDL-C in the near term.

Researchers have recently investigated the impact of lipoproteins other than LDL-C in MACE reduction, including Lp(a) and Apo B [39–41]. The exact mechanisms associated with Lp(a) reduction through PCSK9 inhibition *are* not clearly understood, but LDL receptor, LDL receptor-related protein 1, *and* scavenger receptor class B type 1 are some potential targets affected by PCSK9 inhibitors in Lp(a) catabolism [42]. Additionally, increasing Intermediate Density Lipoprotein and LDL ApoB fractional clearance rate and reducing LDL ApoB production rate have both been proposed as potential mechanisms of *ApoB* decrease by PCSK9 inhibitors [43]. According to our findings, early treatment of PCSK9 inhibitors successfully lowered Lp(a) and Apo B levels. Furthermore, multiple observational studies have found that those with high Lp A levels had a greater risk of MACE [44, 45]. Similarly, the results of previous studies [46–48] indicate a positive correlation between Apo B and the occurrence of MACE. However, the residual cardiovascular risk factors are not well established and further studies with high levels of evidence are necessary to clarify this matter.

Limitations

We acknowledge that our study has limitations. First, in the assessment of MACE, we only have one RCT and three cohorts, which contributed to heterogeneity in our pooled analysis. Second, not enough studies have been conducted to provide preferred evidence of long-term assessment of early injection of evolocumab and alirocumab in ACS patients, probably due to the high cost of PCSK9 inhibitors. Third, considering the absence of data on composite MACE incidence in our included studies, we were unable to analyze it due to the possibility of overlapping MACE components; and finally, our findings could be biased due to the small sample sizes of included studies, especially relevant to MACE, which have a low incidence. Each study used different time frames for *follow-up* and evaluation of outcomes, so we

did not have uniform definitions which *add* to the heterogeneity of our results.

Cost implications and cost-effectiveness

While the clinical benefits of early initiation of PCSK9 inhibitors in ACS patients are engaging, the cost of these drugs is an important barrier to widespread adoption. A study by Gragnano et al. [49] found the rates of patients with full adherence to PCSK9 inhibitors significantly higher than the statin group after mean period of 10.4 months after initiation of the PCSK9 inhibitors. A study by Cesaro et al. [50] found that PCSK9 inhibitor therapy significantly improved EuroQol 5D quality of life scores and visual analog scale health status scores at 1 year compared to baseline in high cardiovascular risk patients, with the greatest improvement seen in the anxiety/depression dimension. The authors postulated that the substantial LDL-C lowering achieved, attainment of recommended LDL goals, less pill burden with injectable therapy, and a sense of reassurance may have contributed to the favorable effects on quality-of-life measures. A recent systematic review by Azari et al. in 2019 highlighted the high cost of PCSK9 inhibitors, reaching $7000 and $15,000 in developed countries and the USA, respectively. However, the review suggested the usage of these drugs may be more cost-effective in different populations [51]. To clarify this knowledge gap further research is needed to assess the cost-effectiveness of early PCSK9 inhibitor use in the post-ACS setting, considering factors such as long-term cardiovascular event reduction, hospital readmissions, and overall healthcare costs.

Conclusions

Early initiation of PCSK9 inhibitors in ACS patients appears to significantly reduce the rate of MI, ACS hospitalization, and the need for revascularization at 6 to 18 months of follow-up. Additionally compared to standard lipid-lowering therapy, more improvement in lipid profile was seen in the PCSK9 inhibitors group. This data supports the utilization of PSCK9 inhibitors earlier in the treatment paradigm of post-ACS patients.

Abbreviations

ACS	Acute coronary syndrome
LDL-C	Low-density lipoprotein cholesterol
PCSK9 inhibitors	Proprotein convertase subtilisin/kexin type 9
IHD	Ischemic heart disease
RCT	Randomized controlled trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
HDL-C	High-density lipoprotein cholesterol
TG	Triglyceride
STEMI	ST elevation myocardial infarction
NSTE	Non ST elevation
RR	Risk ratio
SD	Standard deviation
IQR	Inter-quartile range
CVA	Cerebral vascular accident

Author contributions

Conceptualization, K.H. and H.S.; methodology, K.H.; software, H.S.; validation, S.M. and A.N.; formal analysis, H.S.; investigation, S.M.; data curation, A.N.; writing—original draft preparation S.M. and A.N.; writing—review and editing, K.H., S.T., J.N., and S.H.; visualization, S.M.; project administration S.M. and A.N.; revision J.N and S.H. All authors have read and agreed to the published version of the manuscript.

Data availability

The datasets obtained and analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study did not require ethical approval.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Bergmark BA, Mathenge N, Merlini PA, Lawrence-Wright MB, Giugliano RP. Acute coronary syndromes. Lancet. 2022;399(10332):1347–58.
2. Claessen BE, Guedeney P, Gibson CM, Angiolillo DJ, Cao D, Lepor N, et al. Lipid management in patients presenting with Acute Coronary syndromes: a review. J Am Heart Assoc. 2020;9(24):e018897.

3.   Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.

4.   Schubert J, Lindahl B, Melhus H, Renlund H, Leosdottir M, Yari A, et al. Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study. Eur Heart J. 2020;42(3):243–52.

5.   Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285(13):1711–8.

6.   Chaudhary R, Garg J, Shah N, Sumner A. PCSK9 inhibitors: a new era of lipid lowering therapy. World J Cardiol. 2017;9(2):76–91.

7.   Schwartz GG, Chaitman BR. Initiating PCSK9 inhibition in Hospital for ACS: we can, but does that Mean we should? J Am Coll Cardiol. 2019;74(20):2463–5.

8.   Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Reviews. 2021;10(1):89.

9.   [https://www.crd.york.ac.uk/prospero/#guidancenotes.

10.   https://methods.cochrane.org/bias/resources/
      rob-2-revised-cochrane-risk-bias-tool-randomized-trials.

11.   Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

12.   NOS [Available from. https://www.ohri.ca/programs/clinical_epidemiology/
      oxford.asp.

13.   Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785–805.

14.   Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.

15.   Vavuranakis MA, Jones SR, Ziogos E, Blaha MJ, Williams MS, Foran P, et al. The trajectory of lipoprotein(a) during the Peri- and early postinfarction period and the impact of Proprotein Convertase Subtilisin/Kexin type 9 inhibition. Am J Cardiol. 2022;171:1–6.

16.   Räber L, Ueki Y, Otsuka T, Losdat S, Häner JD, Lonborg J, et al. Effect of Alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with Acute myocardial infarction: the PACMAN-AMI Randomized Clinical Trial. JAMA. 2022;327(18):1771–81.

17.   Okada T, Miyoshi T, Doi M, Nosaka K, Tsushima R, Ugawa S et al. Effect of early initiation of Evolocumab on Lipoprotein(a) in patients with Acute myocardial Infarction: Sub-analysis of a Randomized Controlled Trial. J Cardiovasc Dev Dis. 2022;9(5).

18.   Koskinas KC, Windecker S, Pedrazzini G, Mueller C, Cook S, Matter CM, et al. Evolocumab for early reduction of LDL Cholesterol Levels in patients with Acute Coronary syndromes (EVOPACS). J Am Coll Cardiol. 2019;74(20):2452–62.

19.   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. 2022;63(4):669–77.

20.   Li T, Zhang Y, Cong H. Effect of PCSK9 inhibitor on lipoprotein particles in patients with acute coronary syndromes. BMC Cardiovasc Disord. 2021;21(1):19.

21.   Zhang Y, Zhang Y, Zhang B, Chen Z, Wei Y, Chen P, et al. Early initiation of Evolocumab Treatment in Chinese patients with Acute Coronary Syndrome undergoing percutaneous coronary intervention. Clin Ther. 2022;44(6):901–12.

22.   Yamashita S, Sakamoto A, Shoji S, Kawaguchi Y, Wakabayashi Y, Matsunaga M et al. Feasibility of short-term aggressive lipid-lowering therapy with the PCSK9 antibody in Acute Coronary Syndrome. J Cardiovasc Dev Dis. 2023;10(5).

23.   Zhao Q, Sun S, Zhou F, Yue J, Luo X, Qu X. The inhibition of Evolocumab on non-infarct-related artery disease in patients with ST-Elevation myocardial infarction. Int J Gen Med. 2023;16:2771–81.

24.   Mehta SR, Pare G, Lonn EM, Jolly SS, Natarajan MK, Pinilla-Echeverri N, et al. Effects of routine early treatment with PCSK9 inhibitors in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a randomised, double-blind, sham-controlled trial. EuroIntervention. 2022;18(11):E888–96.

25.   Leucker TM, Blaha MJ, Jones SR, Vavuranakis MA, Williams MS, Lai H, et al. Effect of Evolocumab on atherogenic lipoproteins during the Peri- and early

26.   postinfarction period: a Placebo-Controlled, Randomized Trial. Circulation. 2020;142(4):419–21.

26.   Ji J, Wei X, Chen W, Wan D, Han W, Liu H. Effects of early PCSK9 inhibitor application on inflammation levels and microcirculatory function after PCI in patients with NSTE-ACS. Am J Transl Res. 2023;15(5):3586–96.

27.   Chen H, Chen X. PCSK9 inhibitors for acute coronary syndrome: the era of early implementation. Front Cardiovasc Med. 2023;10:1138787.

28.   Wang Z, Bao Q, Song X, Song H, Wei S, Lv J, et al. Effects of loading-dose statins combined with PCSK9 inhibitor pre-treatment before primary percutaneous coronary intervention on the short-term prognosis in patients with ST-segment elevation myocardial infarction. Cardiovasc Innovations Appl. 2022;7(1):998.

29.   Iannuzzo G, Gentile M, Bresciani A, Mallardo V, Di Lorenzo A, Merone P et al. Inhibitors of protein convertase Subtilisin/Kexin 9 (PCSK9) and Acute Coronary Syndrome (ACS): the state-of-the-art. J Clin Med. 2021;10(7).

30.   Zanchin C, Koskinas KC, Ueki Y, Losdat S, Häner JD, Bär S, et al. Effects of the PCSK9 antibody alirocumab on coronary atherosclerosis in patients with acute myocardial infarction: a serial, multivessel, intravascular ultrasound, near-infrared spectroscopy and optical coherence tomography imaging study-rationale and design of the PACMAN-AMI trial. Am Heart J. 2021;238:33–44.

31.   Nicholls SJ, Kataoka Y, Nissen SE, Prati F, Windecker S, Puri R, et al. Effect of Evolocumab on Coronary Plaque phenotype and burden in statin-treated patients following myocardial infarction. JACC Cardiovasc Imaging. 2022;15(7):1308–21.

32.   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. Can J Cardiol. 2018;34(12):1600–5.

33.   Wang HF, Mao YC, Xu XY, Zhao SY, Han DD, Ge SY, et al. Effect of alirocumab and evolocumab on all-cause mortality and major cardiovascular events: a meta-analysis focusing on the number needed to treat. Front Cardiovasc Med. 2022;9:1016802.

34.   Jarcho JA, Keaney JF. Jr. Proof that lower is Better–LDL cholesterol and IMPROVE-IT. N Engl J Med. 2015;372(25):2448–50.

35.   Krychtiuk KA, Ahrens I, Drexel H, Halvorsen S, Hassager C, Huber K, et al. Acute LDL-C reduction post ACS: strike early and strike strong: from evidence to clinical practice. A clinical consensus statement of the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. Eur Heart Journal: Acute Cardiovasc Care. 2022;11(12):939–49.

36.   Cannon CP. Low-density lipoprotein cholesterol: lower is totally better. J Am Coll Cardiol. 2020;75(17):2119–21.

37.   Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289–367.

38.   Zhao Z, Du S, Shen S, Luo P, Ding S, Wang G, et al. Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia: a frequentist network meta-analysis. Med (Baltim). 2019;98(6):e14400.

39.   Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with lp (a) lipoprotein level and coronary disease. N Engl J Med. 2009;361(26):2518–28.

40.   Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31(23):2844–53.

41.   Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A, et al. Apolipoprotein B particles and Cardiovascular Disease: a narrative review. JAMA Cardiol. 2019;4(12):1287–95.

42.   Kotani K, Banach M. Lipoprotein (a) and inhibitors of proprotein convertase subtilisin/kexin type 9. J Thorac Disease. 2017;9(1):E78.

43.   Reyes-Soffer G, Pavlyha M, Ngai C, Thomas T, Holleran S, Ramakrishnan R, et al. Effects of PCSK9 inhibition with alirocumab on lipoprotein metabolism in healthy humans. Circulation. 2017;135(4):352–62.

44.   Sumarjaya IDGD, Nadha IKB, Lestari AAW. High lipoprotein (a) levels as a predictor of major adverse cardiovascular events in hospitalized-acute myocardial infarction patients. Vasc Health Risk Manag. 2020:125–32.

45.   Chen Z, Jiang C, Qu H, Liang S, Yang J, Wu H, et al. Association of lipoprotein (a) and major adverse cardiovascular events in patients with percutaneous coronary intervention. Archives Med Sci. 2019;15(6):1375–80.

46. Hagström E, Steg PG, Szarek M, Bhatt DL, Bittner VA, Danchin N, et al. Apoli-poprotein B, residual cardiovascular risk after acute coronary syndrome, and effects of alirocumab. Circulation. 2022;146(9):657–72.

47. Ghodsi S, Mohebi M, Sadre-Bafghi SA, Poorhosseini H, Salarifar M, Alidoosti M, et al. Prognostic implications of calculated apo-lipoprotein B in patients with ST-segment elevation myocardial infarction undergoing primary percutane-ous coronary intervention: Outcome is tied to lower cut-points. Clin Cardiol. 2021;44(6):824–32.

48. Zhang C, Ni J, Chen Z, Apolipoprotein B. Displays Superior Predictive Value Than other lipids for long-term prognosis in Coronary Atherosclerosis patients and Particular subpopulations: a retrospective study. Clin Ther. 2022;44(8):1071–92.

49. Gragnano F, Natale F, Concilio C, Fimiani F, Cesaro A, Sperlongano S, et al. Adherence to proprotein convertase subtilisin/kexin 9 inhibitors in high cardiovascular risk patients: an Italian single-center experience. J Cardiovasc Med (Hagerstown). 2018;19(2):75–7.

50. Cesaro A, Gragnano F, Fimiani F, Moscarella E, Diana V, Pariggiano I, et al. Impact of PCSK9 inhibitors on the quality of life of patients at high cardiovas-cular risk. Eur J Prev Cardiol. 2020;27(5):556–8.

51. Azari S, Rezapour A, Omidi N, Alipour V, Behzadifar M, Safari H, et al. Cost-effectiveness analysis of PCSK9 inhibitors in cardiovascular diseases: a systematic review. Heart Fail Rev. 2020;25(6):1077–88.

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