Cardiovascular and safety events of PCSK9 inhibitors in statin-treated patients with cardiovascular risk: A Systematic Review and Meta-Analysis

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ABSTRACT – Objectives: To evaluate whether proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) are associated with cardiovascular and safety events in statin-treated patients with cardiovascular risk. Methods: Electronic databases (Pubmed, Cochrane, MEDLINE, EMBASE, ClinicalTrials.gov) were searched through March 31, 2020. Included randomized clinical trials (RCTs) compared PCSK9i use with no PCSK9i in statin treated patients. Two investigators abstracted data and appraised risks of bias. A meta-analysis was performed to calculate risk ratios (RRs) and 95% CIs using fix-effects models. Adjudicated cardiovascular events (CVE) and adverse drug events (ADE) were defined as the primary outcome. Secondary outcomes were cardiovascular (CV) death, all-cause death, nonfatal myocardial infarction, ischemic stroke, and injection-site reaction. Results: A total of 10 RCTs 50,053 participants were included. PCSK9i use was associated with marginal but significant reductions in the CVE (RR, 0.87 [95%CI, 0.83-0.91]; NNT, 54; P<0.00001; I²=0%, heterogeneity P=0.86), nonfatal myocardial infarction (RR, 0.86 [95% CI, 0.78-0.96]; NNT, 95; P=0.005; I²=0%, heterogeneity P=0.88), and ischemic stroke (RR, 0.75 [95% CI 0.64-0.87]; NNT, 244; P=0.00; I²=0%, heterogeneity P=0.82) compared with no PCSK9i in statin-treated patients with CV risk. No significant difference in ADE were found between statins alone and with PCSK9i. The PCSK9i use was associated with significant increasing in injection-site reaction (RR, 1.55 [95%CI 1.38-1.75]; NNT, 101; P<0.00001; I²=0%, heterogeneity P=0.44). Conclusions: Among statin-treated patients with CV risk, the use of PCSK9is may marginally improve CVE, nonfatal myocardial infarction and ischemic stroke, but had no significant benefit for cardiovascular death, all-cause mortality, ADE and serious ADE. The use of PCSK9is was well tolerated, but had significantly injection-site reactions.

INTRODUCTION

Proprotein convertase subtilisin/kexin type 9 (PCSK9) has been recently discovered as the third gene involved in autosomal dominant hypercholesterolemia. PCSK9 inhibitors (PCSK9is) are novel cholesterol-lowering agents indicated for patients with familial hypercholesterolemia (FH) and/or very highrisk atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C even after maximally tolerated statin therapy (1). PCSK9is are approved in many countries, including the USA, China and across Europe, for the management of patients with hypercholesterolemia on maximally tolerated statin therapy. Studies have shown that PCSK9is reduce LDL-C levels 50% to 60% beyond that
achieved by statin therapy alone (2-6). Randomized controlled trials (RCT) of both PCSK9is alone and in combination with statins have demonstrated a reduced risk for cardiovascular events (CVE) among patients with ASCVD or following acute coronary syndrome (3). Evidence from the FOURIER trial indicates that evolocumab was equally effective in reducing cardiovascular events in ASCVD patients with baseline LDL-C of <70 versus ≥70 mg/dL and among patients who were on maximal- versus submaximal-potency statins (7).

We aimed at assessing the safety of PCSK9is in reducing CV endpoint events in patients with hyperlipidemia. Systematic review and meta-analysis were used to report the cardiovascular events and safety of PCSK9i in hyperlipidemia patients with CV risk, based on RCT.

METHODS

Literature search
The following databases were searched: PubMed, Cochrane, MEDLINE, EMBASE, CNKI, WANFANG data base and CBM; ClinicalTrials.gov, from database inception until 31th March 2020. The following keywords were used: proprotein convertase subtilisin/kexin type 9 (PCSK9), statin, ezetimibe, alirocumab, evolocumab, AMG145, ALN-PCS02, BMS-962476, LY3015014, RG7652, 1D05-IgG2, PF-05335810, REGN727, SAR236553, randomized controlled trial (RCT). Citations were screened at title/abstract level and retrieved as full reports if considered relevant.

Study selection and data management
After removal of duplicates, the titles and abstracts of the search results were screened for relevance by both authors. The final list of included studies was decided on by discussion between authors, with full agreement required before inclusion. No disagreements required resolution by a third reviewer. The main inclusion criteria were (i) randomized control trials including at least 100 participants; (ii) enrolled participants with known cardiovascular risk if they had any of the following: clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndrome (ACS), those with history of myocardial infarction, stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin; systematic coronary risk evaluation (SCORE) 10-year fatal CVD risk ≥1%; past diagnosis of hypertension; (iii) enrolled participants with basic statin treatment; (iv) had a follow-up of at least 8 weeks; (v) compared PCSK9is at any dose with no PCSK9i (defined as placebo or ezetimibe as a positive control); (vi) reported cardiovascular and safety outcomes of interest; (vii) were published in the English language. All patients were under treatment with statins.

Two reviewers (Z.N.Z and Y.T.Z) independently extracted the following information from each study: study acronym; first author; year; trial NCT number; number of participants; main inclusion criteria; mean follow-up duration; intervention (a PCSK9i at any dose) and control treatment (placebo or ezetimibe); patient demographics; mean cholesterol/LDL/HDL; basic statin therapy. Another author X.H. was consulted if there were any discrepancies. If the RCT had more than two groups or factorial designs and permitted multiple comparisons, we extracted only the information and data of interest reported in the original articles.

Outcomes
The primary cardiovascular outcome was adjudicated cardiovascular events. Secondary cardiovascular end points included cardiovascular death, all-cause mortality, nonfatal myocardial infarction, and ischemic stroke. The primary safety outcome was adverse drug events. Secondary safety end points included serious adverse drug events, and injection-site reactions.

Quality assessments
Two authors (Z.N.Z and Y.T.Z) independently assessed the selected studies for quality without blinding to journal or study authorship. Included
RCTs were assessed the risk of bias according to the Cochrane Collaboration’s tool from Cochrane Handbook (8). Discrepancies were resolved by involvement of a third author (X.H.) if required.

**Statistical analysis**

Trial-level data were analyzed according to the original randomization group for which outcome data were available. We performed meta-analysis to calculate risk ratios (RRs), and 95% CIs using the Mantel-Haenszel statistical method. Based on the practice recommendation of the Cochrane Handbook (8), RCTs with zero events in both the intervention and the control groups were not included in the meta-analysis when RRs were calculated.

A fix-effects model was used to pool the data, and statistical heterogeneity between summary data was evaluated using the $I^2$ statistic. Sensitivity analysis was performed by excluding low-quality studies, RCTs recruiting participants with particular conditions, or RCTs with characteristics different from the others.

All meta-analysis were performed using Revman version 5.3 (Cochrane Collaboration). All tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

**RESULTS**

**Literature search**

The systematic search of articles published before March 31, 2020, identified 3839 articles, of which 10 studies were included. In total, 50,568 participants were enrolled. The whole literature search process was summarized in Figure 1.

**Study description**

In 8 RCTs, the patients the control group received placebo plus statin; in 2 RCTs, ezetimibe plus statin. The longest follow-up was 114 weeks, and the mean weighted follow-up was 57.0 weeks. Characteristics of the eligible studies were presented in Table 1.

**Quality of included studies**

Seven factors were used to evaluate the bias of included RCTs according to the Cochrane risk of bias tool (Figure 2). Publication bias of primary outcomes ranging from none to moderate was suggested by visual inspection of the funnel plots or by the linear regression approach (Figure 3). The included trials were not significantly different with regard to risk of bias.

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![Figure 1. Study Flow Chart](image-url)
Table 1. Flowchart of Trial Identification for Meta-analysis

| Source        | Patients (n) | Main inclusion criteria | Follow-up Mean Age | Intervention/n | Control/n | Basic therapy | Primary Outcomes                                                                 |
|---------------|--------------|-------------------------|--------------------|----------------|-----------|---------------|---------------------------------------------------------------------------------|
| Yukawa 2014(9) | 307          | High CV risk hypercholesterolemia | 12 weeks 62 years   | EVB sc: 70 mg Q2W/49; 140 mg Q2W/52; 280 mg QM/51; 420 mg QM/53 | PBO sc Q2W/52; PBO sc QM/50 | ATV, RSV, SIV | CVE, cardiovascular death, all-cause mortality, ADE, serious ADE, injection-site reactions |
| Kereiakes 2015(10) | 316          | high CV risk patients with suboptimally controlled hypercholesterolemia | 52 weeks 63 years   | ALB 75mg sc Q2W/209 | PBO sc Q2W/107 | ATV, RSV, SIV | CVE, cardiovascular death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, all-cause mortality, ADE, serious ADE, injection-site reactions |
| Bays 2015(11) | 355          | hypercholesterolemia at high or very high CVD risk | 24 weeks 63 years   | ALB 75mg sc Q2W/104 | EZB 10mg po Qd/102 | ATV | CVE, cardiovascular death, all-cause mortality, ADE, serious ADE, injection-site reactions |
| Roth 2016(12) | 547          | hypercholesterolemia at moderate-to-very-high CVD risk | 48 weeks 61 years   | ALB 75mg sc Q2W/78 ALB 300mg sc QM/312 | PBO sc Q2W/157 | ATV, RSV, SIV | CVE, cardiovascular death, all-cause mortality, ADE, serious ADE, injection-site reactions |
| Nicholls 2016(13) | 968          | statin-treated patients with 1 major or 3 minor CV risk factors | 76 weeks 60 years   | EVB 420mg sc QM/484 | PBO sc QM/484 | ATV, RSV, SIV, PIV, FLV, PRV, LOV | CVE, nonfatal myocardial infarction, nonfatal stroke, ADE, serious ADE, injection-site reactions |

Table 1 Continues ....
| Study              | N    | Diagnosis/Description                                                                 | n  | Treatment                                      | Placebo Treatment | Outcome                                                                 |
|--------------------|------|---------------------------------------------------------------------------------------|----|-----------------------------------------------|-------------------|-------------------------------------------------------------------------|
| Kiyosue 2016 (14)  | 404  | hyperlipidemia or mixed dyslipidemia and high CV risk                                  | 12 | EVB 140mg sc Q2W/101                          | PBO sc Q2W/101    | ATV, CVE, nonfatal ischemic stroke, cardiovascular death, all-cause mortality, ADE, serious ADE, injection-site reactions |
| Cannon 2015 (15)   | 720  | High CV risk patients with inadequately controlled hypercholesterolaemia              | 104| ALB 75mg sc Q2W: 479 EZB 10mg po Qd: 241    | PBO sc Q2W/101    | ATV, RSV, CVE, cardiovascular death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, all-cause mortality, ADE, serious ADE, injection-site reactions |
| Shahawy 2017 (16)  |      | High CV risk patients with inadequately controlled hypercholesterolaemia              | 104| ALB 75mg sc Q2W: 479 EZB 10mg po Qd: 241    | PBO sc Q2W/101    | ATV, RSV, CVE, cardiovascular death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, all-cause mortality, ADE, serious ADE, injection-site reactions |
| Koh 2018 (17)      | 199  | hypercholesterolemia at high CV risk                                                  | 24 | ALB 75mg sc Q2W/97                           | PBO sc Q2W/102    | ATV, RSV, CVE, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, all-cause mortality, ADE, serious ADE, injection-site reactions |
| Sabatine 2017 (18) | 27564| patients with atherosclerotic CV disease                                              | 114| EVB 140mg sc Q2W or EVB 420mg sc QM/13784    | PBO sc Q2W or PBO sc QM/13780 | ATV, CVE, cardiovascular death, myocardial infarction, ischemic stroke, hemorrhagic stroke, ischemic stroke or transient ischemic attack, all-cause mortality, ADE serious ADE, injection-site reactions |
| Schwartz 2014 (19) | 18924| initiated 1 to 12 months after an index ACS event                                    | 104| ALB 75/150mg sc Q2W/9462                     | PBO sc Q2W/9462   | ATV, RSV, CVE, cardiovascular death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, all-cause mortality, ADE, serious ADE, injection-site reactions |

ACS, acute coronary syndrome; ADE, adverse drug event; ALB, alirocumab; ATV, atorvastatin; CV, cardiovascular; CVD, cardiovascular disease; CVE, cardiovascular event; EVB, evolocumab; EZB, ezetimibe; FLV, Fluvastatin; sc, subcutaneous; LOV, Lovastatin; PBO, placebo; po, per os; PIV, pitavastatin; PRV, pravastatin; Q2W, every 2 weeks; QM, every month; Q2M, every 2 months; RSV, rosuvastatin; SIV, simvastatin.
Quality of included studies
Seven factors were used to evaluate the bias of included RCTs according to the Cochrane risk of bias tool (Figure 2). Publication bias of primary outcomes ranging from none to moderate was suggested by visual inspection of the funnel plots or by the linear regression approach (Figure 3). The included trials were not significantly different with regard to risk of bias.

Figure 2. Risk of bias summary review authors’ judgements about each risk of bias item for each RCT

Figure 3. Publication Bias. Cardiovascular Events of PCSK9i vs placebo (A); Cardiovascular Events of PCSK9i vs ezetimibe (B); adverse drug events of PCSK9i vs placebo (C); adverse drug events of PCSK9i vs ezetimibe (D). Markers represent individual studies
Adjudicated Cardiovascular Events
Eight RCTs were included in the analysis of CVE comparing PCSK9i with placebo. All patients were taking statins. The treatment with a PCSK9i was associated with a marginal but statistically significant decrease in CVE (RR=0.87, [95% CI, 0.83-0.91], NNT=54, P<0.00001; I^2=0%, heterogeneity P=0.86; Figure 4).

Two RCTs were included in the analysis of CVE compared PCSK9i with ezetimibe in statin-treated patients. Compared with ezetimibe, treatment with a PCSK9i was not associated with a statistically significant increase in CVE (RR=1.26, [95% CI, 0.61-2.61], NNT=84, P=0.53; I^2=0%, heterogeneity P=0.85; Figure 5).

Cardiovascular death
Six RCTs were included in the analysis of cardiovascular death compared PCSK9i with placebo in statin-treated patients. Compared with no treatment with a PCSK9i, treatment with a PCSK9i was not associated with a statistically significant decrease in cardiovascular death (RR=0.96, [95% CI, 0.85-1.08], NNT=823, P=0.51; I^2=0%, heterogeneity P=0.38; Figure 6).

Two RCTs were included in the analysis of cardiovascular death compared PCSK9i with ezetimibe in statin-treated patients. Compared with ezetimibe, treatment with a PCSK9i was not associated with a statistically significant decrease in cardiovascular death (RR=0.76, [95% CI, 0.18-3.24], NNT=523, P=0.71; I^2=0%, heterogeneity P=0.54; Figure 7).

All-cause mortality
8 RCTs were included in the analysis of all-cause mortality that compared statins alone with statin plus a PCSK9i. PCSK9is did not significantly reduce all-cause mortality (RR=0.95, [95% CI, 0.86-1.05], NNT=454, P=0.29; I^2=22%, heterogeneity P=0.27; Figure 8).

Two RCTs were included in the analysis of all-cause mortality compared PCSK9i with ezetimibe in statin-treated patients. Compared with ezetimibe, treatment with a PCSK9i was not associated with a statistically significant decrease in all-cause mortality (RR=0.47, [95% CI, 0.16-1.37], NNT=98, P=0.17; I^2=0%, heterogeneity P=0.80; Figure 9).

Figure 4. Forest plot depicting the risk ratios of CVE with PCSK9i versus placebo with statin-treated patients
Figure 5. Forest plot depicting the risk ratios of CVE with PCSK9i versus ezetimibe in statin-treated patients

Figure 6. Forest plot depicting the risk ratios of cardiovascular death with PCSK9i versus placebo in statin-treated patients

Figure 7. Forest plot depicting the risk ratios of cardiovascular death with PCSK9i versus ezetimibe in statin-treated patients

Figure 8. Forest plot depicting the risk ratios of all-cause mortality with PCSK9i versus placebo in statin-treated patients
Nonfatal myocardial infarction

4 RCTs were included in the analysis of nonfatal myocardial infarction in patients taking statin versus statin plus a PCSK9i. The treatment with a PCSK9i was associated with a small but statistically significant decrease in nonfatal myocardial infarction (RR=0.86, [95% CI, 0.78-0.96], NNT=95, P=0.005; I²=0%, heterogeneity P=0.88; Figure 10).

Ischemic stroke

4 RCTs were included in the analysis of ischemic stroke compared PCSK9i with placebo in statin-treated patients. PCSK9i treatment was associated with a marginal but statistically significant decrease in ischemic stroke (RR=0.75, [95% CI, 0.64-0.87], NNT=244, P=0.00; I²=0%, heterogeneity P=0.82; Figure 11).

Adverse Drug Events

Eight RCTs were included in the analysis of ADE compared PCSK9i with placebo in statin-treated patients. Compared with the statin only treatment, a PCSK9i treatment was not associated with a statistically significant decrease in ADE (RR=0.99, [95% CI, 0.98-1.00], NNT=155, P=0.16; I²=47%, heterogeneity P=0.07; Figure 12).

Two RCTs were included in the analysis of ADE compared PCSK9i with ezetimibe in statin-treated patients. The treatment with a PCSK9i was not associated with a statistically significant increase in ADE (RR=1.05, [95% CI, 0.96-1.15], NNT=26, P=0.31; I²=0%, heterogeneity P=0.72; Figure 13).

Figure 9. Forest plot depicting the risk ratios of all-cause mortality with PCSK9i versus ezetimibe in statin-treated patients

Figure 10. Forest plot depicting the risk ratios of nonfatal myocardial infarction with PCSK9i versus placebo in statin-treated patients
Figure 11. Forest plot depicting the risk ratios of nonfatal myocardial infarction with PCSK9i versus placebo in statin-treated patients

Figure 12. Forest plot depicting the risk ratios of adverse drug events with PCSK9i versus placebo in statin-treated patients

Figure 13. Forest plot depicting the risk ratios of adverse drug events with PCSK9i versus ezetimibe in statin-treated patients

**Serious Adverse Drug Events**

Eight RCTs were included in the analysis of serious ADE compared PCSK9i with placebo in statin-treated patients. Compared with no treatment with a PCSK9i, treatment with a PCSK9i was not associated with a statistically significant decrease in serious ADE (RR=0.97, [95% CI, 0.94-1.01], NNT=114, P=0.10; I²=36%, heterogeneity P=0.14; Figure 14).

Two RCTs were included in the analysis of serious ADE compared PCSK9i with ezetimibe in statin-treated patients. Compared with ezetimibe, treatment with a PCSK9i was not associated with a statistically significant decrease in serious ADE (RR=1.00, [95% CI, 0.73-1.37], NNT=67, P=0.99; I²=2%, heterogeneity P=0.31; Figure 15).
Injection-site reaction

Nine RCTs were included in the analysis of injection-site reaction compared PCSK9i with oral forms in statin-treated patients. Compared with oral forms, treatment with a PCSK9i was associated with a statistically significant increase in serious ADE (RR=1.55, [95% CI, 1.38-1.75], NNT=101, P<0.00001; P=0%, heterogeneity P=0.44; Figure 16).

**Figure 14.** Forest plot depicting the risk ratios of serious adverse drug events with PCSK9i versus placebo in statin-treated patients

**Figure 15.** Forest plot depicting the risk ratios of serious adverse drug events with PCSK9i versus ezetimibe in statin-treated patients

**Figure 16.** Forest plot depicting the risk ratios of injection-site reaction with PCSK9i versus placebo or ezetimibe in statin-treated patients
DISCUSSION

In this meta-analysis of 10 RCTs enrolling 50,053 statin-treated participants with cardiovascular risk, PCSK9i use was associated with marginal reductions in the CVE, nonfatal myocardial infarction, and ischemic stroke. The use of injectable PCSK9is was associated with an increased risk of injection-site reactions.

PCSK9 is a serine protease crucially involved in determining circulating LDL-C levels by controlling the expression of LDLR on the surface of hepatocytes through a post-transcriptional mechanism (19). Dubuc et al (20) performed a study showed that the NARC-1 gene, PCSK9, was identified as the third locus implicated in autosomal dominant hypercholesterolemia which was strongly induced by statins in a dose-dependent manner.

PCSK9is are fully human monoclonal antibody that binds to and inhibits PCSK9 (21). Two Food and drug administration (FDA)-approved monoclonal antibody PCSK9i-alirocumab and evolocumab have demonstrated significant LDL-C lowering and improved outcomes in patients with ASCVD when used as adjuncts to maximally tolerated statin therapy (3, 22).

As monotherapy, alirocumab can reduce LDL-C as much as intensive statin treatment (23) and in conjunction with statin, alirocumab greatly enhances LDL-C lowering (24, 25). Treatment with alirocumab has been generally well tolerated, with occasional, mild local injection site reactions in homozygous familial hypercholesterolemia (HoFH) and ASCVD patients.

Evolocumab reduces LDL cholesterol levels by approximately 60% (26-28). Evolocumab has received the approval by the FDA and the European Medicines Agency, as a therapeutic agent for HoFH, primary hypercholesterolemia or dyslipidemia in 2015 (29-31).

The co-published guidelines for the management of dyslipidemia (32) of European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) in 2019 confirmed that the lipid modification can reduce cardiovascular risk. Guideline showed that for the ACS patients, PCSK9i should be considered as early as possible in patients who have received the maximum tolerated dose of statin and ezetimibe but whose LDL-C levels are not up to standard. In 2017, the National Lipid Association recommended that for the ASCVD patients, especially if there are additional risk factors, PCSK9is may be combined with statins to reduce ASCVD risk after LDL-C ≥ 70mg/dL after treatment with or without the maximum tolerated dose of statin. (33) PCSK9i may be considered to further reduce LDL-C levels in patients with advanced ASCVD who receive a maximum tolerated dose of statins with or without ezetimibe and have LDL-C levels of 70mg/Dl. Practical guidelines for PCSK9is for patients at high cardiovascular risk issued by the ESC/EAS working group in 2017 (34) recommended PCSK9i as primary and secondary preventive therapies for patients with cardiovascular disease.

Karatasakis et al. conducted a meta-analysis (35) on the efficacy and safety of PCSK9i in patients with overall hypercholesterolemia. Results showed that PCSK9i can improve CV outcomes in the treatment of hypercholesterolemia. Casula et al. (36) compared the efficacy of PCSK9i with placebo in the overall population. Results showed that the addition of PCSK9i can significantly reduce the incidence of CVE myocardial infarction and stroke. Different from previous studies, our study limited the inclusion population, as associated CV risk and statins were used as the primary treatment in all the included studies. This design allows for a more precise comparison of the efficacy and safety of adding PCSK9is to statins in people with CV risk. Similar to the above results, our study showed that the addition of PCSK9i can significantly reduce the incidence of CVE, non-fatal myocardial infarction and
ischemic stroke. Our study also conducted a meta-analysis on cardiovascular death and all-cause death, but the results showed that PCSK9i could not significantly improve event outcome. This results suggest that the addition of a PCSK9i may provide some benefit for people at high risk of myocardial infarction and stroke. The addition of PCSK9is showed no significant advantage in CVE, cardiovascular death or all-cause death comparing with statin combined ezetimibe. It is noted that the study, ODYSSEY OPTIONS I and ODYSSEY COMBO II, involved a small number of people.

For safety outcomes, PCSK9i would not increase the incidence of ADE and severe ADE comparing with placebo or ezetimibe. However, as a class of drugs that require subcutaneous injections, PCSK9is can cause injection-site reactions which would affect the acceptability and compliance of this product in clinical application.

Limitations
Some limitations of our study deserve mention. First, because the PCSK9 inhibitors are relatively new and not widely studied, we were not able to analysis the different doses. Second, some RCTs did not described CVE in details. Third, there were different in follow-up period between RCTs. Fourth, although the sample size we included was large, in the results with statistically significant, 95% CI were close to 1 which indicated a small difference. Whether the results have clinical importance remains to be further studied.

CONCLUSIONS
First, our study which included a large size of population demonstrated that the addition of PCSK9is on classical statin therapy could marginally but statistically significantly reduce CVE, nonfatal myocardial infarction and ischemic stroke rateamong patients with CV risk. But there were no significant benefit in cardiovascular death, all-cause mortality, ADE and serious ADE. Second, as there were only two RCTs analyzed the efficacy and safety between PCSK9i and ezetimibe on statin-treated patients at present, it is too early to draw a conclusion about this comparsion. Third, PSCK9is had obvious injection-site reaction which was tolerated. Above all, this study provides some support for the benefit of actively adding PCSK9is on the basis of statins therapy to further reduce some CVE in patients with CV risk.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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