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Reduction of C-reactive protein, low-density lipoprotein cholesterol, and its relationship with cardiovascular events of different lipid-lowering therapies

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: To evaluate the reductions of C-reactive protein (CRP) and low-density lipoprotein cholesterol (LDL-C) in different lipid-lowering drugs, and to assess the relationships between the reductions of CRP, LDL-C, and cardiovascular (CV) events.

Methods: We searched MEDLINE, EMBASE, and Cochrane CENTRAL up to September 1, 2021. Randomized controlled trials (RCTs) comparing statins, proprotein convertase subtilisin/kexin type 9 monoclonal antibodies (PCSK9-mAbs), or ezetimibe against placebo with a treatment duration of at least 4 weeks and data on the effects of cholesterol-lowering interventions on LDL-C and CRP were included in this meta-analysis. The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated.

Results: Compared with placebo treatment, statins and ezetimibe treatments resulted in a significant decrease in LDL-C level (statins: WMD –47.94 mg/dL, 95% CI –51.21 to –44.67 mg/dL; ezetimibe: WMD –22.84 mg/dL, 95% CI –26.76 to –18.92 mg/dL) and CRP level (statins: WMD –0.67 mg/L, 95% CI –0.90 to –0.45 mg/dL; ezetimibe: –0.64 mg/L, 95% CI –1.07 to –0.21 mg/dL). Compared with placebo treatment, treatment with PCSK9-mAbs resulted in significant decrease in LDL-C level (WMD –54.24 mg/dL, 95% CI –59.77 to –48.70 mg/dL), while the concentration of CRP did not decrease significantly. Meta-regression analysis showed no significant association between change in CRP level and change in LDL-C level. Subgroup comparisons suggested that treatment with PCSK9-mAbs showed a greater reduction in LDL-C level when compared with the statins group and ezetimibe group, while the risks of CV death, myocardial infarction (MI), and stroke showed no significant differences.

Conclusion: Based on the current study, our results suggested that statins, ezetimibe, and PCSK9-mAbs are effective in reducing LDL-C levels. Treatment with statins and ezetimibe also demonstrated a significant effect on CRP. The traditional lipid-lowering strategy including statin and ezetimibe showed similar benefit on CV outcomes compared with the PCSK9-mAbs treatment.

Abbreviations: 3P-MACE = three-point major adverse cardiovascular event, 4P-MACE = four-point major adverse cardiovascular event, CI = confidence interval, CRP = C-reactive protein, CV = cardiovascular, CVD = cardiovascular disease, CVOT = cardiovascular outcome trial, hs-CRP = high-sensitivity CRP, IL = interleukin, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, PCSK9-mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody, RCT = randomized controlled trial, RR = risk ratio, SD = standard deviations, WMD = weighted mean difference.

Keywords: cardiovascular disease, C-reactive protein, ezetimibe, low-density lipoprotein cholesterol, PCSK9-mAb, statin

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1. Introduction

Cardiovascular disease (CVD) is caused mainly by atherosclerosis, which is the leading cause of mortality worldwide. Low-density lipoprotein cholesterol (LDL-C) is a well-recognized atherogenic lipoprotein, which initiates the process of vascular inflammation and has been the major target for lipid-lowering therapy.[1] Among the lipid-lowering agents available, statins are the cornerstones since their effects of anti-atherosclerosis have been proven in population with or without established CVD.[2–7] Proprotein convertase subtilisin/kexin type 9 monoclonal antibody (PCSK9-mAb) is an emerging class of LDL-C lowering agent, which brings about a greater reduction in LDL-C than statins.[8–11] The benefits on risk of CVD were found in several randomized controlled trials (RCTs).[12–16] In the whole, the relationship between reduction of LDL-C level and decreased risk of CVD under cholesterol-lowering agents is well established.

Inflammation is an independent risk factor for manifestations of atherosclerosis and plays important roles in the underlying pathological process of atherosclerosis. This point of view was supported by several RCTs. In the Cardiovascular Risk Reduction Study (CANTOS), the interleukin (IL)-1β inhibitor canakinumab was shown to reduce the total number of cardiovascular events significantly in patients with prior myocardial infarction (MI) and evidence of residual inflammatory risk.[17] Colchicine appeared to be effective for the prevention of cardiovascular events in patients with coronary disease in the COLchicine Cardiovascular Outcomes Trials (COLCOT),[18] Low Dose Colchicine (LoDoCo) trial, and LoDoCo2 trial.[19] The independent effect of inflammation in the process of atherosclerosis was also illustrated by a recent meta-analysis revealing that the use of biological disease-modifying antirheumatic drugs with potent anti-inflammatory effects might be associated with reduced risks of CV events in patients with systemic inflammatory conditions.[20] C-reactive protein (CRP) is a well-recognized indicator, which can reflect the extent of inflammation. Previous results showed that achieving lower CRP levels was associated with better CV outcomes in patients receiving statin treatments.[21–23] While some other studies argued that there is no association between the achieved CRP and the reduced risk of CV events.[24,25] In addition to the inconsistent evidence, the concomitant reduction of LDL-C makes it difficult to conclude a causal role of inflammation in atherothrombotic events. Moreover, it was controversial that whether the anti-atherosclerotic effect under cholesterol-lowering agents is mainly dependent on the LDL-C reduction or the improvement of inflammation.

In this context, we try to evaluate the reductions of CRP and LDL-C in different use of lipid-lowering drugs, and to assess the relationships between the reductions of CRP or LDL-C with CV events.

2. Methods

The included and excluded studies were collected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[26] As a meta-analysis, the ethical review was not applicable.

Studies were identified by a literature search of MEDLINE® (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE®. The literature was searched from inception to September 1, 2021. The following terms were searched: statins, rosuvastatin, atorvastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, lovastatin, PCSK9-mAb, alirocumab, evolocumab, LY2015014, RG7652, ezemitibe, CRP, high-sensitivity CRP (hs-CRP), and RCTs. We also searched ClinicalTrial.gov to confirm LDL-C and CRP change for eligible published trials. Only literature published in English were searched.

Studies were included if they met the following inclusion criteria: RCTs comparing statins, PCSK9-mAbs, or ezetimibe against placebo; with a treatment duration of at least 4 weeks; with data on the effects of cholesterol-lowering interventions on LDL-C and CRP; studies enrolled adult participants (age ≥18 years)with metabolic syndrome or related disorders with metabolic diseases, including hypercholesterolemic, diabetes mellitus, coronary artery disease, hypertension, chronic kidney disease, polycystic ovary syndrome, obesity, and microalbuminuria. The exclusion criteria were: non-clinical studies; observational studies with a cross-sectional, case-control or cohort design; studies in which changes in LDL-C and CRP levels were not reported; the participants with conditions that affect the levels CRP, such as infection, injury, etc.

Two review authors (YWJ and LC) independently extracted the following data from each study using a standardized form: publication data (title, first author, publication year), study design, baseline characteristics of the study population (numbers of patients included in the RCTs, gender proportion, age), description of the study drugs and their dosage, treatment duration, levels of LDL-C at baseline, levels of CRP at baseline, levels of LDL-C after treatment, and levels of CRP after treatment. The events CV death, MI, stroke, and the composite endpoint were also extracted. The composite endpoint consisted the three-point major adverse cardiovascular event (3P-MACE, including MI, stroke, and CV death) and the four-point major adverse cardiovascular event (4P-MACE, including MI, stroke, heart failure, and all-cause mortality). Disagreements or discrepancies were resolved by discussion among the 2 reviewers and a third investigator (CXL). The quality of the included RCTs was evaluated by 2 independent authors (YWJ and LC) using the Cochrane Collaboration risk of bias tool, including selection bias, performance bias, detection bias, reporting bias and others. Publication bias was assessed by a funnel plot.

LDL-C concentrations were calculated in $mg \cdot dL^{-1}$. CRP concentrations were calculated in $mg \cdot L^{-1}$. Mean and standard deviations (SDs) were collected for the changes in LDL-C and CRP levels after treatment for each included study. The SDs were calculated using the methods described by Sahebkar et al.[27] If the outcome measures were reported as the median and inter-quartile range, they were switched to mean and SD first using the methods described by Hozo et al.[28] The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for LDL-C changes and CRP changes from baseline using the RevMan software (version 5.3, Nordic Cochrane Centre, Copenhagen, Denmark). The risk ratio (RR) and 95% CI were calculated for the risk of CV death, MI, stroke, and composite endpoint. Heterogeneity of the effect across studies was assessed by Q^2 statistics, which are distributed as χ^2 statistics. Results with a P value <.05 indicated a lack of homogeneity among risks. The I^2 statistic was used to quantify the percent of total variation across studies that was attributable to heterogeneity rather than to chance. A value of >50% represented substantial variability. Fixed effects and random effects models were used with low and high levels of heterogeneity, respectively. A meta-regression model of the average mean differences in LDL-C and CRP was used to assess the relationship between average LDL-C changes and average CRP changes with adjustment of age, gender, BMI, baseline LDL-C level, baseline CRP level. The meta-regression analyses were conducted using STATA software (version 11.0, StataCorp., College Station, Texas, USA). The relationships between changes in LDL-C level and risk of CV events, changes in CRP level and risk of CV events were also assessed by the method of meta-regression.

3. Results

A search of the literature yielded 6723 potentially eligible studies. After exclusion, 68 studies met the inclusion criteria and

were analyzed in the meta-analysis. Among these studies, 49 studies compared treatment with statin and a placebo; 9 studies compared treatment with ezetimibe and a placebo, and 9 studies compared treatment with PCSK9-mAb and a placebo. One study compared the treatment of both statin and ezetimibe versus placebo. The selection process is summarized in Figure 1, Supplemental Digital Content 1, http://links.lww.com/MD/H310. The characteristics of included studies are shown in Table 1, Supplemental Digital Content 2, http://links.lww.com/MD/H311. The assessment of bias showed that the majority of the included studies have a low risk (Figure S2, Supplemental Digital Content 3, http://links.lww.com/MD/H312). This meta-analysis was registered in the PROSPERO platform as CRD42021284208.

3.1. Changes of LDL-c from baseline in different lipid-lowering therapies

Compared with placebo treatment, the use of statins led to a significantly greater change in the level of LDL-C (WMD −47.94 mg/dL, 95% CI −51.21 to −44.67 mg/dL, $P < .001$; Table 1, Figure S3, Supplemental Digital Content 4, http://links.lww.com/MD/H313). When compared with placebo, the use of ezetimbe led to a significantly greater decrease in the level of LDL-C (WMD −22.84 mg/dL, 95% CI −26.76 to −18.92 mg/dL, $P < .001$; Table 1, Figure S3, Supplemental Digital Content 4, http://links.lww.com/MD/H313). Compared with placebo, the use of PCSK9-mAbs also resulted in a significantly greater decrease in the level of LDL-C (WMD −54.24 mg/dL, 95% CI −59.77 to −48.70 mg/dL, $P < .001$; Table 1, Figure S3, Supplemental Digital Content 4, http://links.lww.com/MD/H313). The subgroup comparisons for LDL-C level between different lipid-lowering therapies showed no significant difference between statins and PCSK9-mAb treatments ($P = .05$), while both of comparisons between statins and ezetimibe, comparisons between PCSK9-mAb and ezetimibe showed significant difference ($P < .001$).

3.2. Changes of CRP from baseline in different lipid-lowering therapies

Compared with placebo treatment, the use of statins led to a significantly greater change in the level of CRP (WMD −0.67 mg/L, 95% CI −0.90 to −0.45 mg/dL, $P < .001$; Table 2, Figure S4, Supplemental Digital Content 5, http://links.lww.com/MD/H314). When compared with placebo, the use of ezetimibe also led to a significantly greater decrease in the level of CRP (WMD −0.64 mg/L, 95% CI −1.07 to −0.21 mg/dL, $P = .003$; Table 2, Figure S4, Supplemental Digital Content 5, http://links.lww.com/MD/H314). When compared with placebo, the use of PCSK9-mAbs did not lead to a significant change in the level of CRP (WMD −0.06 mg/dL, 95% CI −0.17 to 0.05 mg/dL, $P = .32$; Table 2, Figure S4, Supplemental Digital Content 5, http://links.lww.com/MD/H314). The subgroup comparisons for CRP level between different lipid-lowering therapies showed significant difference ($P < .001$).

3.3. CV outcomes in different lipid-lowering therapies

Compared with placebo treatment, the use of statin showed a 35% reduced risk of MI with significance (RR 0.65, 95% CI 0.47–0.88, $P = .005$), but a 19% reduced risk of CV death, a 24% reduced risk of stroke, and a 18% reduced risk of the composite endpoint risk without significance (RR 0.81, 95% CI 0.56–1.17, $P = .26$; RR 0.76, 95% CI 0.42–1.39, $P = .38$; RR 0.92, 95% CI 0.63–1.34, $P = .65$; respectively; Table 3).

Compared with placebo treatment, the use of PCSK9-mAb showed a 27% reduced risk of MI (RR 0.73, 95% CI 0.65–0.82, $P < .001$) and a 21% reduced risk of stroke (RR 0.79, 95% CI 0.66–0.94, $P = .01$) with significance, but a 57% reduced risk of CV death without significance (RR 0.43, 95% CI 0.04–5.30, $P = .51$; Table 3).

Compared with placebo treatment, the use of ezetimibe showed a 13% reduced risk of MI (RR 0.87, 95% CI 0.81–0.95, $P = .001$) with significance, but a 14% reduced risk of stroke (RR 0.86, 95% CI 0.74–1.00, $P = .05$) without significance, and no reduced risk of CV death (RR 1.00, 95% CI 0.89–1.12, $P = .98$; Table 3).

Table 1

Analyses for the use of lipid-lowering therapies and LDL-C change.

Treatment	Participant	WMD (mg/dL)	95% CI (mg/dL)	*P* value	I^2 (%)	Subgroups difference (*P* value)
Statins	18,785/17,668	−47.94	−51.21 to −44.67	<.001	98	<.001
Ezetimibe	9872/9886	−22.84	−26.76 to −18.92	<.001	93	
PCKS9-mAbs	15,865/15,593	−54.24	−59.77 to −48.70	<.001	100	

CI = confidence interval, LDL-C = low-density lipoprotein cholesterol, PCSK9-mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody, WMD = weighted mean difference.

Table 2

Analyses for the use of lipid-lowering therapies and CRP change.

Treatment	Participant	WMD (mg/L)	95% CI (mg/L)	*P* value	I^2 (%)	Subgroups difference (*P* value)
Statins	18,785/17,668	−0.67	−0.90 to −0.45	<.001	97	<.001
Ezetimibe	9872/9886	−0.64	−1.07 to −0.21	.003	74	
PCKS9-mAbs	15,789/15,401	−0.06	−0.17 to 0.05	.32	46	

CI = confidence interval, CRP = C-reactive protein, PCSK9-mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody, WMD = weighted mean difference.

Table 3

Analyses for the use of lipid-lowering therapies and CV outcomes.

Treatment	Endpoint	Participant (lipid-lowering therapies/placebo)	RR	95% CI	*P* value	I^2 (%)
Statins	MI	15,710/15,640	0.65	0.47–0.88	.005	67
	Stroke	12,261/12,264	0.76	0.42–1.39	.38	75
	CV death	12,870/12,413	0.81	0.56–1.17	.26	78
	Composite endpoint	15,132/15,134	0.92	0.63–1.34	.65	93
PCSK9-mAbs	MI	14,631/14,455	0.73	0.65–0.82	<.001	0
	Stroke	14,268/14,264	0.79	0.66–0.94	.01	0
	CV death	14,261/13,867	0.43	0.04–5.30	.51	64
Ezetimibe	MI	9474/9488	0.87	0.81–0.95	.001	0
	Stroke	9424/9440	0.86	0.74–1.00	.05	0
	CV death	9424/9440	1.00	0.89–1.12	.98	0

CI = confidence interval, CRP = C-reactive protein, CV = cardiovascular, MI = myocardial infarction, PCSK9-mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody, RR = risk ratio.

3.4. Relationships between changes of LDL-c or CRP and CV outcomes

After adjusting by the age, gender, and smoking status, results of meta-regression analysis suggested that the change of LDL-C was not associated with the risks of CV death, MI, stroke, or the composite endpoint with the use of lipid-lowering drugs (Table S2, Supplemental Digital Content 6, http://links.lww.com/MD/H315). Change of CRP was not associated with the risks of CV death, MI, stroke, or the composite endpoint either (Table S3, Supplemental Digital Content 7, http://links.lww.com/MD/H316).

3.5. Relationships between LDL-c level change and CRP concentration

After adjusting by the age, gender, BMI, baseline LDL-C level, and baseline CRP level, results of meta-regression analysis showed that the changes of LDL-C was not associated with the changes of CRP concentration with statins treatment, PCSK9-mAbs treatment or ezetimibe treatment. In the subgroup analysis using CRP and hs-CRP concentration measurements separately, the results were consistent with that using the combined CRP concentration (Table S4, Supplemental Digital Content 8, http://links.lww.com/MD/H317).

Comparisons for LDL-C level and CV outcomes between the conventional lipid-lowering strategies including statins and ezetimibe, and PCSK9-mAb treatment group.

As treatment with statins and ezetimibe both showed reduction in CRP concentration, we further combined statins and ezetimibe as the conventional lipid-lowering group to compare with the PCSK9-mAbs treatment group. Result of comparison between these 2 groups suggested that treatment with PCSK9-mAbs showed a greater reduction in LDL-C level when compared with the conventional lipid-lowering treatment group ($P = .009$; Table 4). However, the comparisons for the risks of CV death, MI, and stroke showed no significant differences between the conventional lipid-lowering treatment group and PCSK9-mAbs treatment group($P < .05$; Table 5).

Table 4

Subgroup comparisons for the LDL-C level.

Treatment	Participant	WMD (mg/dL)	95% CI (mg/dL)	*P* value	I^2 (%)	Subgroups difference (*P* value)
Conventional lipid-lowering strategies (including statins and ezetimibe)	28,657/27,554	−44.44	−49.27 to −39.62	<.001	99	.009
PCKS9-mAbs	15,865/15,593	−54.24	−59.77 to −48.70	<.001	100	

CI = confidence interval, LDL-C = low-density lipoprotein cholesterol, PCSK9-mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody, WMD = weighted mean difference.

4. Discussion

This meta-analysis revealed that reduction in LDL-C levels and CRP concentration showed heterogeneity between statin, ezetimibe, and PCSK9-mAbs treatments. The risk of MI was improved significantly under the treatment of all the lipid-lowering therapies, while the improvement in stroke was only found under the treatment of PCSK9-mAbs. The risk of composite endpoint and CV death revealed a trend of reduction, while no statistical significance was reached. Results of meta-regression analysis showed no association between CRP change and risk of CV events.

In a previous meta-analysis study on statin therapy, reduction of CRP concentration was not found to be associated with reduced CV risk and mortality.[29] Another meta-analysis on statin mono-therapy and statin adding on ezetimibe therapy revealed that baseline CRP concentration was associated with the benefits of LDL-C lowering on MI, but not on MACE, stroke or mortality outcomes, whereas achieved and magnitude of reduction in CRP did not have an association.[30] These findings seem to be consistent with the present meta-analysis. However, we should interpret the result with caution, as some of the included studies were not cardiovascular outcome trials (CVOTs) with emerged CV benefits, and the CRP level was only tested in part of the participants in the limited included CVOTs.

Relationship between changes in LDL-C levels and risk of CV events was not found in the results of meta-regression analysis, which is not consistent with the results of previous studies. The possible reason for this inconsistency might be the difference in inclusion criteria. As mentioned above, some of the included studies in the current meta-analysis were not CVOTs with primary endpoint of CV events and long follow-up duration, so that their effects on CV events might be still ahead.

Linear association between changes in LDL-C level and CRP concentration was not demonstrated in this study. This result suggested that the anti-inflammation effect of statins and ezetimibe is independent of their effect on the reduction of LDL-C level. In the reanalysis of CVOTs, including the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT TIMI-22) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the maximal benefit was observed in participants achieving reduced levels of both variables, instead of the participants with reduced levels of single one,[31–33] which also implied the independent action of cholesterol-lowering and anti-inflammation. From the aspect of pathological changes modulated by statin therapies, both cholesterol dependent and cholesterol independent mechanisms had been revealed.[31] Theses evidence all suggested that the lipid-lowering effects on LDL-C and CRP levels might be independent.

Table 5

Subgroup comparisons for the CV outcomes.

Treatment	Endpoint	Participant	RR	95% CI	*P* value	I^2 (%)	Subgroups difference (*P* value)
Conventional lipid-lowering strategies (including statins and ezetimibe)	CV death	22,294/21,853	0.87	0.70–1.08	.20	71	.59
PCKS9-mAbs		14,261/13,867	0.43	0.04–5.30	.51	64	
Conventional lipid-lowering strategies (including statins and ezetimibe)	MI	25,184/25,128	0.83	0.77–0.89	<.001	61	.89
PCKS9-mAbs		14,631/14,455	0.73	0.65–0.82	<.001	0	
Conventional lipid-lowering strategies (including statins and ezetimibe)	Stroke	21,685/21,704	0.79	0.57–1.10	.17	59	.98
PCKS9-mAbs		14,268/14,264	0.79	0.66–0.94	.01	0	

CI = confidence interval, CRP = C-reactive protein, CV = cardiovascular, MI = myocardial infarction, PCSK9-mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibody, RR = risk ratio.

In this meta-analysis, we further combined the lipid-lowering agents with CRP-lowering properties—statins and ezetimibe, to make comparison with the lipid-lowering agents without observed CRP-lowering properties—PCSK9-mAbs, to explore the effects of CRP-lowering on CV outcomes. The results suggested that treatment with PCSK9-mAbs was associated with greater reduction in LDL-C level when compared with the treatment of statins plus ezetimibe, while similar effects on CV outcomes were found in the statins plus ezetimibe groups as compared with the intensive lipid-lowering group with PCSK9-mAbs. Based on these results, we inferred that the anti-inflammation effect of statins and ezetimibe might make up the benefits on cardiovascular disease to some extent. Therefore, we proposed that patients not accessing of PCSK9-mAbs might also obtain similar cardiovascular protective effect with the treatment of statins or statins plus ezetimibe. The traditional lipid-lowering treatment might be more suitable for the general patients from the perspective of health economics.

Despite the current evidence basically supported that pleiotropic mechanisms contribute to the effects on CV risk, there has been ongoing debate as to whether the observed benefits of lipid-lowering therapies are mediated mainly via LDL-C lowering properties. As no association between reduction in CRP concentration and reduced CV risk was observed, and the independent relationship between changes in LDL-C levels and CRP levels, we speculated that the LDL-C lowering effect might play the dominant role. By using the method of Egger regression, a reanalysis of randomized trial evidence also suggested that the cardiovascular benefits of statins were mediated primarily via their LDL-C lowering properties rather than by any pleiotropic effects.[34]

The present meta-analysis had several potential limitations. First, as this meta-analysis was aimed to explore the association between CRP levels and CV risk and the change in LDL-C level, the enrolled studies should provide both of the LDL-C data and the CRP data. Therefore, CVOTs without CRP measurements were excluded, which might lower the ability to detecting the CV risk. In this case, the relationship between CV events and CRP level, LDL-C level could not be fully revealed. Additionally, we pooled the results of a group of studies that were not originally intended to evaluate the CRP level. Second, some early study used the CRP level, instead of hs-CRP level, which might lower the sensitivity of measurements and cause bias to the results. Third, difference exists in the characteristics of participants, definition of MI, stroke, CV death, and composite endpoint in the enrolled studies, which might lead to heterogeneity across studies. Fourth, as the most of the included studies on PCSK9-mAbs comprised a run-in phase with statin therapy, which is known to mitigate the vascular inflammatory response, the baseline CRP levels might not fully represent the residual inflammation risk; In addition, the included RCTs on PCSK9-mAbs were largely developed in participants with familial hypercholesterolemia who tend to have normal level of CRP, in which population that the inflammation is not the dominant pathogenesis. Hence, the results should be interpreted with caution.

5. Conclusion

In conclusion, statins, PCSK9-mAbs, and ezetimibe are all effective in reducing LDL-C level. Among these, treatment with PCSK9-mAbs was associated with a greater reduction. Treatment with statins and ezetimibe also demonstrated a significant effect on CRP levels. Benefits in MI risk were observed in all the treatment groups. Significant association between CV risk, changes in LDL-C levels, and changes in CRP levels were not found in this meta-analysis. The traditional lipid-lowering strategy with statin and ezetimibe showed similar benefit on CV outcomes compared with the intensive lipid-lowering strategy with PCSK9-mAbs. Future head-to-head studies comparing the traditional lipid-lowering strategies and intensive lipid-lowering strategy are needed to verify the observations of this meta-analysis. Moreover, more CVOTs with measurements of CRP levels and longer durations are needed to elucidate the relationship between inflammation and CV outcomes.

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Author contributions

Linong Ji conceived and designed the review. Wenjia Yang, Chu Lin, Fang LV, Xingyun Zhu identified reports and extracted data. Xiaoling Cai and Xueyao Han provided statistical advice and contributed to data interpretation. Wenjia Yang drafted the manuscript. All authors read and approved the final manuscript.

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