

Effect of lipid-lowering therapies on C-reactive protein levels: a comprehensive meta-analysis of randomized controlled trials

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Abstract

Chronic low-degree inflammation is a hallmark of atherosclerotic cardiovascular (CV) disease. To assess the effect of lipid-lowering therapies on C-reactive protein (CRP), a biomarker of inflammation, we conducted a meta-analysis according to the PRISMA guidelines. Databases were searched from inception to July 2023. Inclusion criteria were: (i) randomized controlled trials (RCTs) in human, Phase II, III, or IV; (ii) English language; (iii) comparing the effect of lipid-lowering drugs vs. placebo; (iv) reporting the effects on CRP levels; (v) with intervention duration of more than 3 weeks; (vi) and sample size (for both intervention and control group) over than 100 subjects. The between-group (treatment-placebo) CRP absolute mean differences and 95% confidence intervals were calculated for each drug class separately. A total of 171 668 subjects from 53 RCTs were included. CRP levels (mg/L) were significantly decreased by statins [−0.65 (−0.87 to −0.43), bempedoic acid; −0.43 (−0.67 to −0.20), ezetimibe; −0.28 (−0.48 to −0.08)], and omega-3 fatty acids [omega3FAs, −0.27 (−0.52 to −0.01)]. CRP was reduced by −0.40 (−1.17 to 0.38) with fibrates, although not statistically significant. A slight increase of CRP concentration was observed for proprotein convertase subtilisin/kexin type 9 inhibitors [0.11 (0.07–0.14)] and cholesteryl-ester transfer protein inhibitors [0.10 (0.00–0.21)], the latter being not statistically significant. Meta-regression analysis did not show a significant correlation between changes in CRP and LDL cholesterol (LDL-C) or triglycerides. Statins, bempedoic acid, ezetimibe, and omega3FAs significantly reduce serum CRP concentration, independently of LDL-C reductions. The impact of this anti-inflammatory effect in terms of CV prevention needs further investigation.

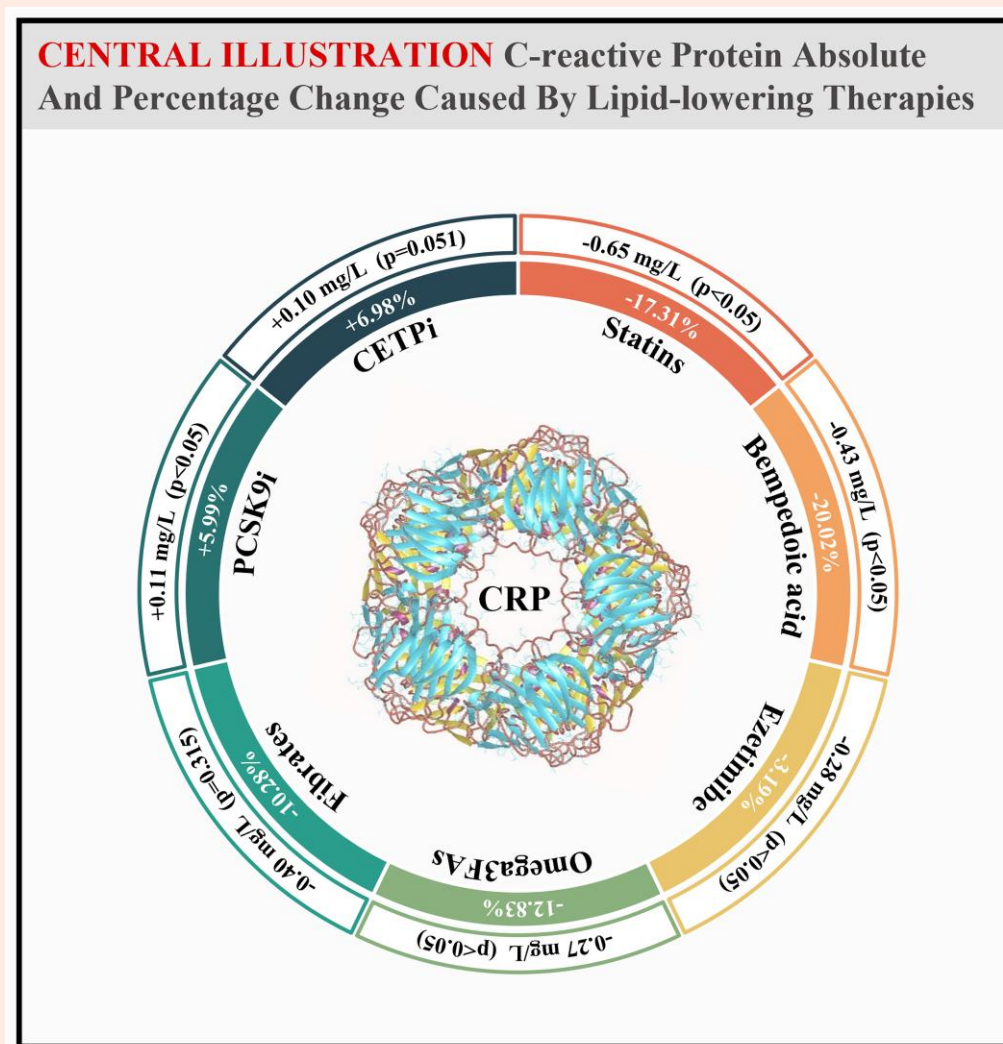
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Graphical Abstract



Keywords

C-reactive protein • Lipid-lowering therapies • Cardiovascular disease • Inflammation

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains one of the leading causes of death and disability. Controlling LDL cholesterol (LDL-C) levels is the cornerstone of the prevention of cardiovascular (CV) events.¹ Lipid-lowering therapy (LLT) with statins as the first choice, is commonly used to improve arterial health and prevent atherosclerosis. Nevertheless, data from both clinical trials and registries highlighted that even under optimized LLT, many patients continue to suffer CV events.² It has been suggested that the inflammatory state that typically characterizes ASCVD³ could be responsible for this residual CV risk. Thus, the evaluation of inflammatory biomarkers, such as C-reactive protein (CRP), could be critical.⁴ Indeed, even though the causal role of CRP in the atherosclerotic process has been excluded by Mendelian randomization studies,⁵ CRP concentration in serum still is a useful marker of the inflammatory status of a given patient. Observational studies reported the link between increased high-sensitivity CRP levels and an elevated risk of CV disease (CVD) in individuals with or without a CVD history.⁶ Moreover, several clinical trials, including PROVE-IT⁷ (atorvastatin

80 mg) and IMPROVE-IT⁸ (ezetimibe plus simvastatin 40 mg), illustrated that patients who met both targets (LDL-C <70 mg/dL and CRP <2 mg/L) had better clinical outcomes.

From this point of view, it is of extreme interest to understand whether LLTs have an effect also on inflammatory markers and how much this could be related to the lipid-lowering effect of these drugs. Therefore, we aimed to perform a comprehensive evaluation of the anti-inflammatory effect, as determined by the effect on CRP plasma levels of several LLTs [including statins, ezetimibe, omega-3 fatty acids (omega3FAs), fibrates, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), cholesteryl-ester transfer protein inhibitors (CETPi), bempedoic acid], and to assess whether this effect is associated to the reduction of LDL-C or triglycerides (TG) levels.

2. Methods

We conducted a meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁹ (see [Supplementary material online, Table S1](#)).

2.1 Study selection and eligibility criteria

Inclusion criteria were: (i) randomized controlled trials (RCTs) in humans, Phase II, III, or IV; (ii) English language and full text available (studies published as abstracts were excluded); (iii) comparing the effect of lipid-lowering drugs to placebo (addition of the same drug to both intervention and control group was acceptable); (iv) reporting the effects on CRP levels; (v) with intervention duration of more than 3 weeks; (vi) and sample size (for both intervention and control group at randomization) over than 100 subjects. Patients with inflammatory diseases and autoimmune diseases were excluded.

All selected articles were independently screened by two researchers, with minor differences resolved by discussion and consultation with a third researcher.

2.2 Search strategy and information sources

PubMed, EMBASE, Web of Science, CENTRAL, and ClinicalTrial.gov were searched from inception to July 2023. The following keywords were combined for literature searches: 'randomized controlled trials', 'C-reactive protein', 'statins', 'bempedoic acid', 'ezetimibe', 'omega-3 fatty acids', 'fibrates', 'PCSK9 inhibitors', 'CETP inhibitors' (searching strategies are shown in detail in [Supplementary material online, File S1](#)).

2.3 Data extraction and quality assessment

Two independent investigators extracted the data using a predefined data collection form including the first author; year of publication; country; the number of participants and their main characteristics [e.g. sex, mean age; type of prevention (primary or secondary)]; intervention duration; treatment (name and dosage) and control; mean or median values and variance [standard deviation (SD), standard error (SE), interquartile range (IQR), 95% confidence interval (95% CI), the minimum and maximum values (range), *P*-value (*P*)] both at baseline and follow-up or absolute change for CRP, LDL-C and TG concentrations.

Authors were contacted by email to obtain information not available in the published articles.

Quality assessment of the included RCTs was performed using the Jadad scale,¹⁰ calculating a score ranging from 0 (very poor) to 13 points (rigorous).

2.4 Data synthesis and statistical analysis

The between-group (treatment-placebo) absolute mean differences in CRP, LDL-C, and TG levels and their 95% CI were calculated for each drug class. CRP was recorded in mg/L, whereas LDL-C and TG were recorded in mg/dL (or converted from mmol/L through dividing by 0.0259 or 0.0113¹¹ for LDL-C and TG, respectively). All data were presented as mean and SD. We used median values for CRP and TG since they were not normally distributed, and converted SE, IQR, 95% CI, range, and *P* (when it was displayed as within-group *P* and a specific number) to SD by using formulas recommended by the Cochrane Handbook.¹² Since the within-group absolute mean difference was computed by subtracting the baseline level from the follow-up level, 0.5 was used as the correlation coefficient to calculate pooled SD within groups.¹³ For trials that reported variances at baseline but without any information for variances at follow-up, the variances at baseline were also used for follow-up. Multiple intervention groups were combined into a single intervention group when they were compared with only one control group in the trial. Pooled estimates were assessed by using both the fixed-effects and the random-effects models. The generic inverse variance method was used to balance the heterogeneity between studies, and the restricted maximum likelihood estimator was used to estimate the between-study variance.¹⁴ When significant heterogeneity was discovered (as determined by Cochrane's *Q* test and the *I*² statistic,¹⁵ *P* < 0.05), the results from the random-effects model were presented.

An influence analysis was conducted by omitting one study at a time, to determine how much a single study influenced the overall results.¹⁶

Potential publication bias was visually assessed through funnel plot asymmetry,¹⁷ also quantitatively evaluated by Begg's rank correlation¹⁸ and Egger's weighted regression tests.¹⁹

Subgroup analyses were conducted based on the background of patients (primary or secondary prevention, or mixed), and baseline CRP levels [low (<3 mg/L) or high (≥3 mg/L)].

Finally, we performed mixed-effects meta-regression analyses to investigate the potential link between LDL-C or TG absolute change and CRP absolute change, also adjusting for relevant covariates (including age, sex, and intervention duration), for each drug class separately.

All tests were considered statistically significant for *P*-value < 0.05. The analyses and the corresponding graphical visualization of forest and funnel plots were conducted using R (version 4.0.5).

3. Results

3.1 Characteristics of included studies

The flow chart indicating the procedure of literature searching and study screening is shown in [Supplementary material online, Figure S1](#), while a list of excluded trials is provided in [Supplementary material online, Table S2](#). A total of 171 668 subjects from 53 RCTs were included in our meta-analysis (15 RCTs for statins, 9 RCTs for omega3FAs, 8 RCTs for ezetimibe, 7 RCTs for PCSK9i, 6 RCTs for fibrates and CETPi, and 5 RCTs for bempedoic acid). [Table 1](#) and [Supplementary material online, Table S3](#) summarize the main characteristics of included studies. Sample sizes of the included studies ranged from 200 to 26 145 participants. The intervention duration ranged between 1.5 and 60 months. All studies were shown in high methodological quality, with the Jadad score ranging from 8 to 13 points (see [Supplementary material online, Table S4](#)).

3.2 Meta-analysis results

The different effects on CRP concentration among LLTs are shown in [Figures 1](#) and [2](#). An additional −0.65 mg/L (−0.87 to −0.43) absolute reduction of CRP concentration was observed with statins compared with the placebo group. Bempedoic acid showed a considerable lowering effect on CRP levels as well [−0.43 mg/L (−0.67 to −0.20)]. CRP was also reduced by −0.28 mg/L (−0.48 to −0.08) in the ezetimibe-combined treatment group compared with the single-statin treatment group. A similar absolute decrease was obtained with omega3FAs [−0.27 mg/L (−0.52 to −0.01)] compared with placebo. In addition, a −0.40 mg/L (−1.17 to 0.38) lowering in CRP level was observed in patients treated with fibrates, although not statistically significant. PCSK9i [0.11 mg/L (0.07–0.14)] and CETPi [0.10 mg/L (0.00–0.21)] both showed a small rise in CRP levels; however, the latter was not statistically significant.

[Supplementary material online, Figures S2](#) and [S3](#) report the pooled analyses on absolute differences in LDL-C and TG levels, respectively. LDL-C concentration was markedly reduced by PCSK9i [−61.98 mg/dL (−73.53 to −50.42)] and statins −48.37 mg/dL (−55.71 to −41.03)]. Bempedoic acid, ezetimibe, and CETPi reduced LDL-C levels by −25.04 mg/dL (−30.96 to −19.12), −22.09 mg/dL (−30.10 to −14.08) and −21.90 mg/dL (−30.19 to −13.61), respectively. A slight decrease in LDL-C was shown with fibrates [−5.56 mg/dL (−10.38 to −0.75)], while the change of LDL-C with omega-3FAs was not significant [−0.96 mg/dL (−3.84 to 1.92)]. All these LLTs significantly reduced TG levels from −10.58 mg/dL (−12.40 to −8.76) with ezetimibe to −53.55 mg/dL (−78.91 to −28.20) with fibrates, except for bempedoic acid [0.61 mg/dL (−1.64 to 2.86)].

No publication bias was found when evaluating funnel plot asymmetry through quantitative analysis (Begg's rank correlation and Egger's linear regression tests) for each outcome (see [Supplementary material online, Figures S4–S6](#) and [Table S5](#)).

Influence analyses illustrated that no appreciable impact on pooled estimates for CRP concentration was observed omitting one study at a time for statin, bempedoic acid, ezetimibe, or fibrate trials,

Table 1 Characteristics of the 53 trials included in the analysis

Trial name	Year published	Primary or secondary prevention	Experimental group		Control group		Intervention duration (months)	Baseline CRP levels (mg/L)
			N	Intervention	N	Intervention		
Statins								
CARE	1999	Secondary	258	Pravastatin 40 mg	214	Placebo	60	2.30
AFCAPS/TexCaps	2001	Primary	2885	Lovastatin 20–40 mg	2834	Placebo	12	1.60
PRINCE	2001	Primary	865	Pravastatin 40 mg	837	Placebo	6	2.00
MIRACL	2003	Secondary	1186	Atorvastatin 80 mg	1216	Placebo	4	11.50
Athyros et al. (2005)	2005	Primary	100	Atorvastatin 20 mg + fenofibrate 200 mg	100	Fenofibrate 200 mg	12	4.50
DIACOR	2006	Primary	100	Simvastatin 20 mg + fenofibrate 160 mg	100	Fenofibrate 160 mg	3	2.24
4D	2008	Mixed	539	Atorvastatin 20 mg	544	Placebo	6	5.80
GISSI-HF	2008	Secondary	336	Rosuvastatin 10 mg	314	Placebo	3	2.68
JUPITER	2008	Primary	8901	Rosuvastatin 20 mg	8901	Placebo	12	4.20
AURORA	2009	Mixed	1389	Rosuvastatin 10 mg	1384	Placebo	3	4.80
CORONA(1)	2009	Secondary	777	Rosuvastatin 10 mg	779	Placebo	3	1.10
CORONA(2)	2009	Secondary	1711	Rosuvastatin 10 mg	1694	Placebo	3	5.50
ASTRONOMER	2010	Primary	134	Rosuvastatin 40 mg	135	Placebo	3	1.60
CARDS	2015	Primary	1174	Atorvastatin 10 mg	1148	Placebo	12	1.30
LIPID	2015	Secondary	3854	Pravastatin 40 mg	3889	Placebo	12	2.47
HOPE-3	2016	Primary	785	Rosuvastatin 10 mg	769	Placebo	36	3.60
Bempedoic acid								
CLEAR harmony	2019	Mixed	1421	Bempedoic acid 180 mg	724	Placebo	3	1.49
CLEAR serenity	2019	Mixed	218	Bempedoic acid 180 mg	103	Placebo	3	2.92
CLEAR wisdom	2019	Mixed	467	Bempedoic acid 180 mg	240	Placebo	3	1.61
Ballantyne et al. (2020)—BA	2020	Mixed	101	Bempedoic acid 180 mg	52	Placebo	3	2.95
Ballantyne et al. (2020)—BA + EZE	2020	Mixed	102	Bempedoic acid + ezetimibe 10 mg	102	Ezetimibe 10 mg	3	3.12
CLEAR outcomes	2023	Primary	2100	Bempedoic acid 180 mg	2106	Placebo	12	2.39
Ezetimibe								
ENHANCE	2008	Mixed	357	Ezetimibe 10 mg + simvastatin 80 mg	363	Simvastatin 80 mg	24	1.70
Kouvelos et al. (2013)	2013	Mixed	126	Ezetimibe 10 mg + rosuvastatin 10 mg	136	Rosuvastatin 10 mg	12	3.15
IMPROVE-IT	2015	Secondary	6954	Ezetimibe 10 mg + simvastatin 40 mg	7019	Simvastatin 40 mg	12	9.60
PRECISE-IVUS	2015	Secondary	100	Ezetimibe 10 mg + atorvastatin	102	Atorvastatin	10	3.00
CuVIC	2017	Secondary	109	Ezetimibe 10 mg + statins	112	Statins	6	4.46
HIJ-PROPER	2017	Secondary	673	Ezetimibe 10 mg + pitavastatin 2 mg	691	Pitavastatin 2 mg	12	9.20
I-ROSETTE	2018	Mixed	195	Ezetimibe 10 mg + rosuvastatin 5/10/20 mg	194	Rosuvastatin 5/10/20 mg	2	0.70
Ballantyne et al. (2020)—EZE	2020	Mixed	102	Ezetimibe 10 mg	52	Placebo	3	3.03

Continued

Table 1 Continued

Trial name	Year published	Primary or secondary prevention	Experimental group		Control group		Intervention duration (months)	Baseline CRP levels (mg/L)
			N	Intervention	N	Intervention		
Ballantyne <i>et al.</i> (2020)—EZE + BA	2020	Mixed	102	Ezetimibe 10 mg + bempedoic acid 180 mg	101	Bempedoic acid 180 mg	3	3.12
Omega-3 fatty acids								
GISSI-HF	2008	Secondary	551	EPA/DHA 1 g	559	Placebo	36	2.39
DO IT	2009	Mixed	247	EPA/DHA 2.4 g	239	Placebo	36	3.58
ANCHOR	2012	Mixed	444	E-EPA 2/4 g	219	Placebo	3	2.05
ALPHA OMEGA	2014	Secondary	601	EPA/DHA 0.4 g	609	Placebo	40	1.46
ESPRIT	2015	Secondary	416	OM3-CA 2/4 g	211	Placebo	1.5	4.05
HEARTS	2017	Secondary	129	EPA/DHA 3.36 g	111	Placebo	30	0.90
VITAL	2019	Primary	1644	EPA/DHA 1 g	1636	Placebo	48	1.60
STRENGTH	2020	Mixed	1467	OM3-CA 4 g	1499	Placebo	12	2.10
REDUCE-IT	2022	Mixed	3322	E-EPA 4 g	3229	Placebo	24	2.18
Fibrates								
Athyros <i>et al.</i> (2005)	2005	Primary	100	Fenofibrate 200 mg + atorvastatin 20 mg	100	Atorvastatin 20 mg	12	4.50
DIACOR	2006	Primary	100	Fenofibrate 160 mg + simvastatin 20 mg	100	Simvastatin 20 mg	3	2.24
Zhu <i>et al.</i> (2006)	2006	Primary	115	Fenofibrate 160 mg + hypotensive agents	110	Hypotensive agents	24	6.73
BIP	2007	Secondary	1319	Bezafibrate 400 mg	1297	Placebo	24	3.40
DAIS	2016	Mixed	108	Fenofibrate 200 mg	96	Placebo	36	1.80
Ihm <i>et al.</i> (2020)	2020	Mixed	174	Fenofibrate 160 mg + pitavastatin 2 mg	173	Pitavastatin 2 mg	2	7.00
PCSK9 inhibitors								
DESCARTES	2014	Mixed	535	Evolocumab 420 mg	276	Placebo	13	1.00
RUTHERFORD-2	2015	Mixed	210	Evolocumab 140 or 420 mg	101	Placebo	3	1.01
GLAGOV	2016	Secondary	484	Evolocumab 420 mg	484	Placebo	19	1.60
FOURIER	2018	Secondary	13 091	Evolocumab 140 or 420 mg	13 054	Placebo	12	1.70
SPIRE-1 and 2	2018	Mixed	9738	Bococizumab 150 mg	9785	Placebo	3.5	1.88
EVOPACS	2019	Secondary	141	Evolocumab 420 mg	150	Placebo	2	6.68
PACMAN-AMI	2022	Secondary	126	Alirocumab 150 mg	132	Placebo	13	6.40
CETP inhibitors								
ILLUMINATE	2007	Mixed	7533	Torcetrapib 60 mg	7534	Placebo	3	1.30
ILLUSTRATE	2007	Secondary	464	Torcetrapib 60 mg	446	Placebo	24	2.10
RADIANCE 1	2007	Mixed	423	Torcetrapib 60 mg	427	Placebo	24	0.80
DEFINE	2010	Mixed	779	Anacetrapib 100 mg	773	Placebo	6	1.40
dal-VESSEL	2012	Mixed	206	Dalcetrapib 600 mg	209	Placebo	9	2.65
ACCELERATE	2017	Secondary	4558	Evacetrapib 130 mg	4565	Placebo	3	1.52

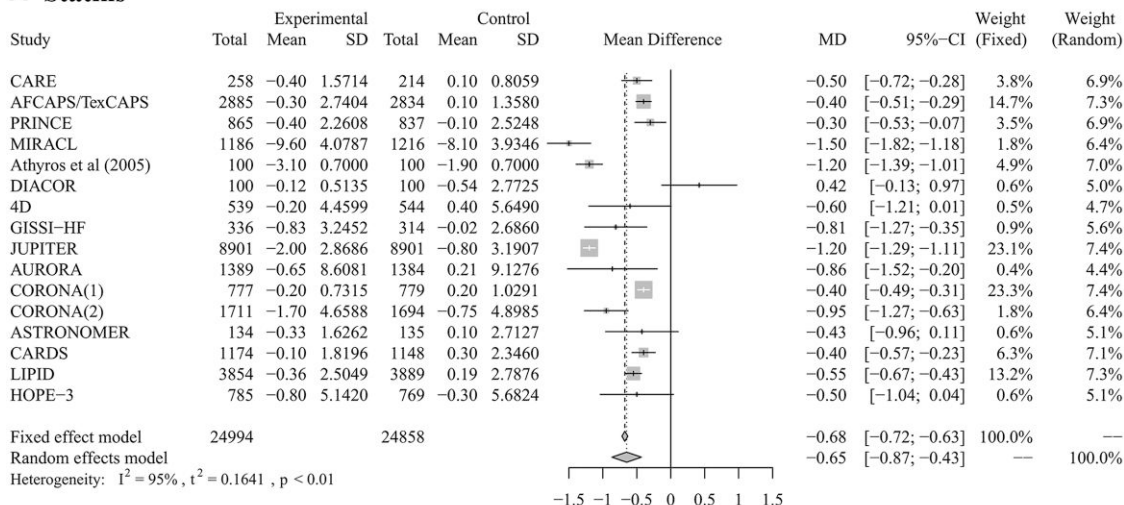
DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; E-EPA, eicosapentaenoic acid ethyl ester; OM3-CA, omega-3 carboxylic acid.

respectively. However, the effect on CRP levels caused by omega3FAs became smaller but still statistically significant after removing the REDUCE-IT trial [−0.13 mg/L (−0.19 to −0.06)]. The increase in CRP level caused by PCSK9i became not statistically significant after removing FOURIER [0.07 mg/L (−0.04 to 0.18)] or SPIRE-1 and 2 [0.06 mg/L (−0.01 to 0.13)], while the increase in CRP level caused by CETPi turned out to be statistically significant after removing ILLUSTRATE trial [0.13 mg/L (0.01–0.25)] (see [Supplementary material online, Figures S7 and S8](#)).

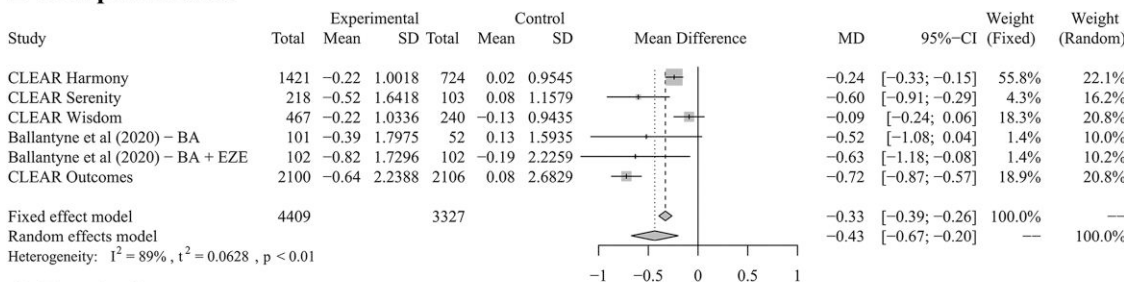
3.3 Subgroup analyses

For statins, subgroup analyses illustrated a slight difference in CRP reduction between patients in primary or secondary prevention [−0.53 mg/L (−0.89 to −0.18) vs. −0.76 mg/L (−1.09 to −0.44), respectively], albeit not statistically significant ($P = 0.63$). After statins therapy, the decrease in CRP level in the group of participants with higher CRP levels at baseline was greater than the reduction in subjects with a baseline CRP level of <3 mg/L [−1.05 mg/L (−1.29 to −0.82) vs. −0.43 mg/L (−0.50 to −0.36); $P < 0.01$].

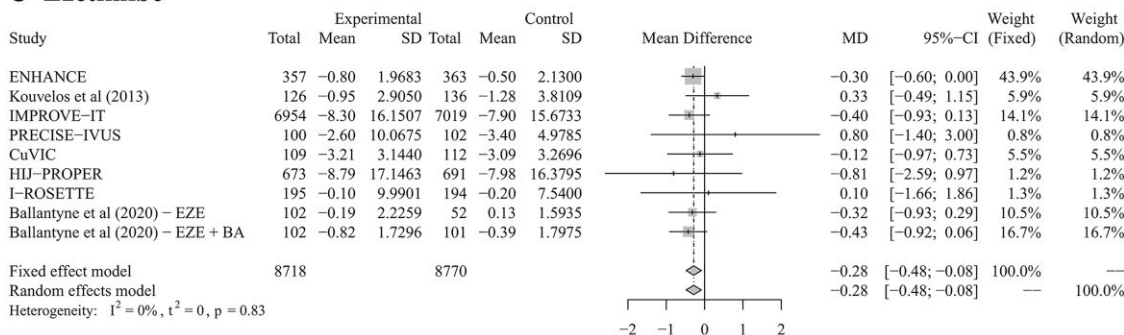
A Statins



B Bempedoic acid



C Ezetimibe



D Omega3FAs

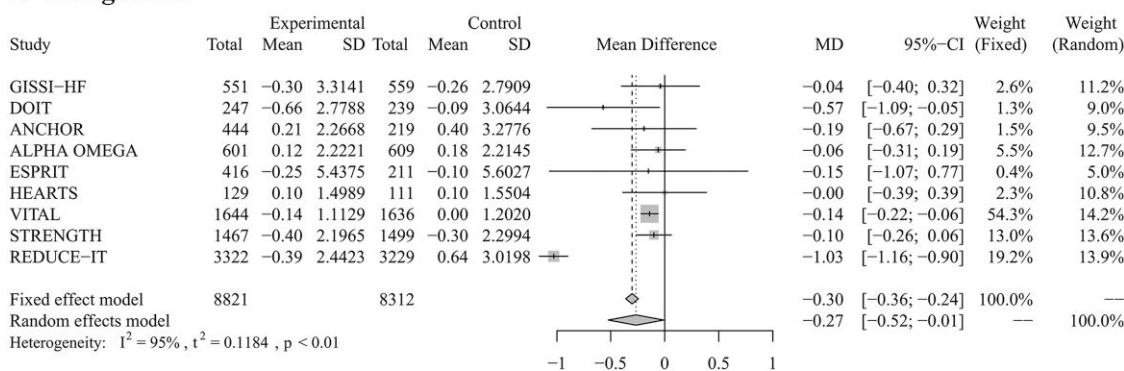
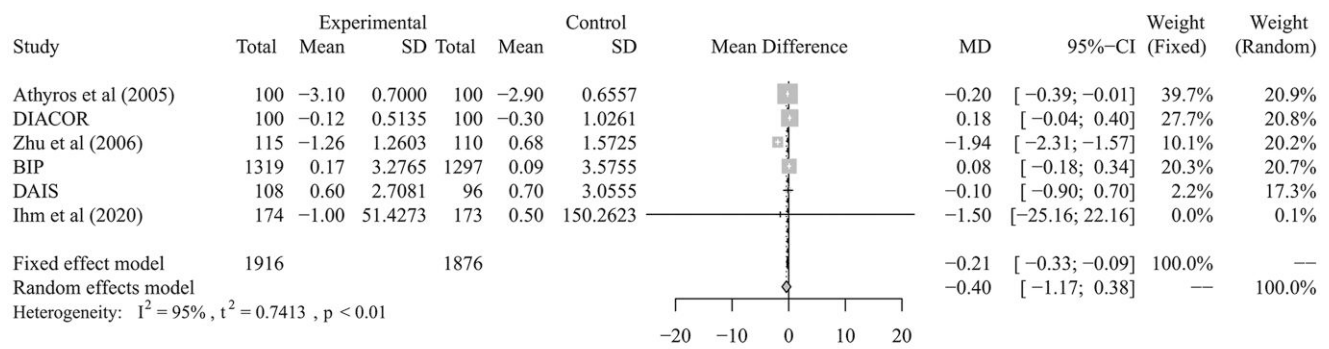
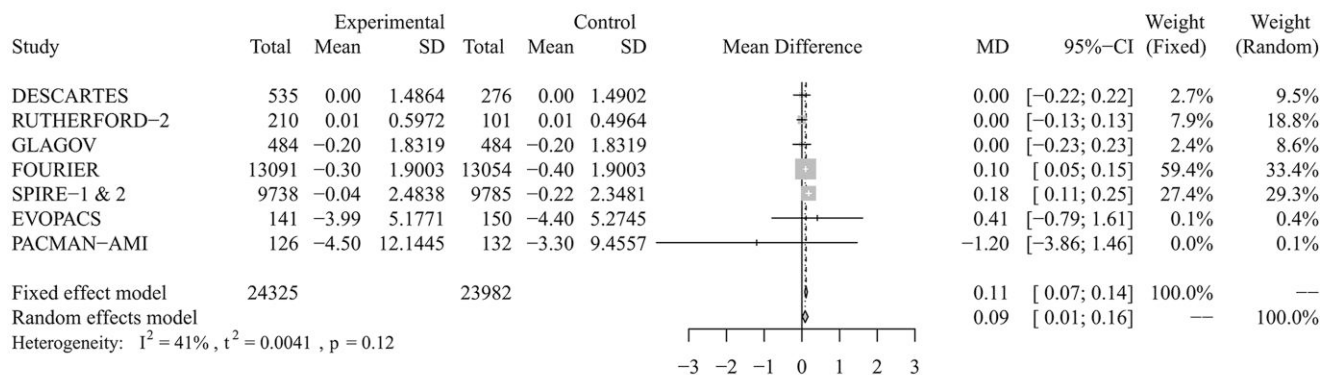


Figure 1 Forest plots indicate the significant lowering effect on CRP levels caused by statins (A), bempedoic acid (B), ezetimibe (C), and omega3FAs (D). The trials are sorted by published year. The pooled estimate and 95% CIs were represented by the centre line and lateral tips of the diamond and shown in absolute mean differences (mg/L). CI, confidence interval; MD, mean difference; SD, standard deviation.

A Fibrates



B PCSK9i



C CETPi

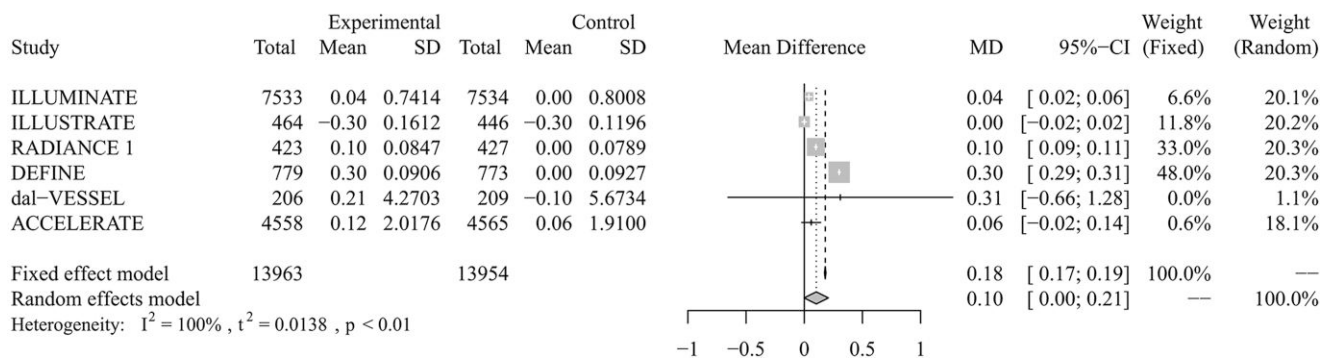


Figure 2 Forest plots indicate the not significant lowering or increasing effect on CRP levels related to fibrates (A), PCSK9 inhibitors (B), and CETPi (C). The trials are sorted by published year. The pooled estimate and 95% CIs were represented by the centre line and lateral tips of the diamond and shown in absolute mean differences (mg/L). CI, confidence interval; MD, mean difference; SD, standard deviation.

For omega3FAs, subgroup analyses discovered little difference in CRP lowering among patients in primary or secondary prevention and patients with low or high CRP levels at baseline, but none of them were statistically significant. Similar results were also found for ezetimibe, fibrates, and PCSK9i.

Additionally, subgroup analysis of CETPi failed to show a statistically significant difference between trials involving only patients in secondary prevention and trials involving patients either in primary or secondary prevention ($P = 0.17$). All these data are shown in *Figure 3*.

3.4 Meta-regression analysis

Among LLTs with a significant effect on CRP levels, mixed-effects meta-regression did not show a significant correlation between changes in CRP and LDL-C levels or between changes in CRP and TG levels even after adjustment by age, sex, and intervention duration, except for

omega3FAs (slope for the adjusted model: 0.0879, $P < 0.0001$, [Supplementary material online, Table S6](#), and slope for the adjusted model: 0.0371, $P < 0.0001$, [Supplementary material online, Table S7](#)). However, when the REDUCE-IT trial was removed from the meta-regression analyses, both the correlations became not statistically significant (data not shown).

4. Discussion

Atherosclerosis is now considered to be primarily a progressive inflammatory disease. As some reports suggested modulating effects on inflammatory markers by LLTs, we systematically evaluated evidence in literature and conducted the largest, most comprehensive, and up-to-date meta-analysis (53 RCTs) on the effect of LLTs on CRP, in addition to lipid

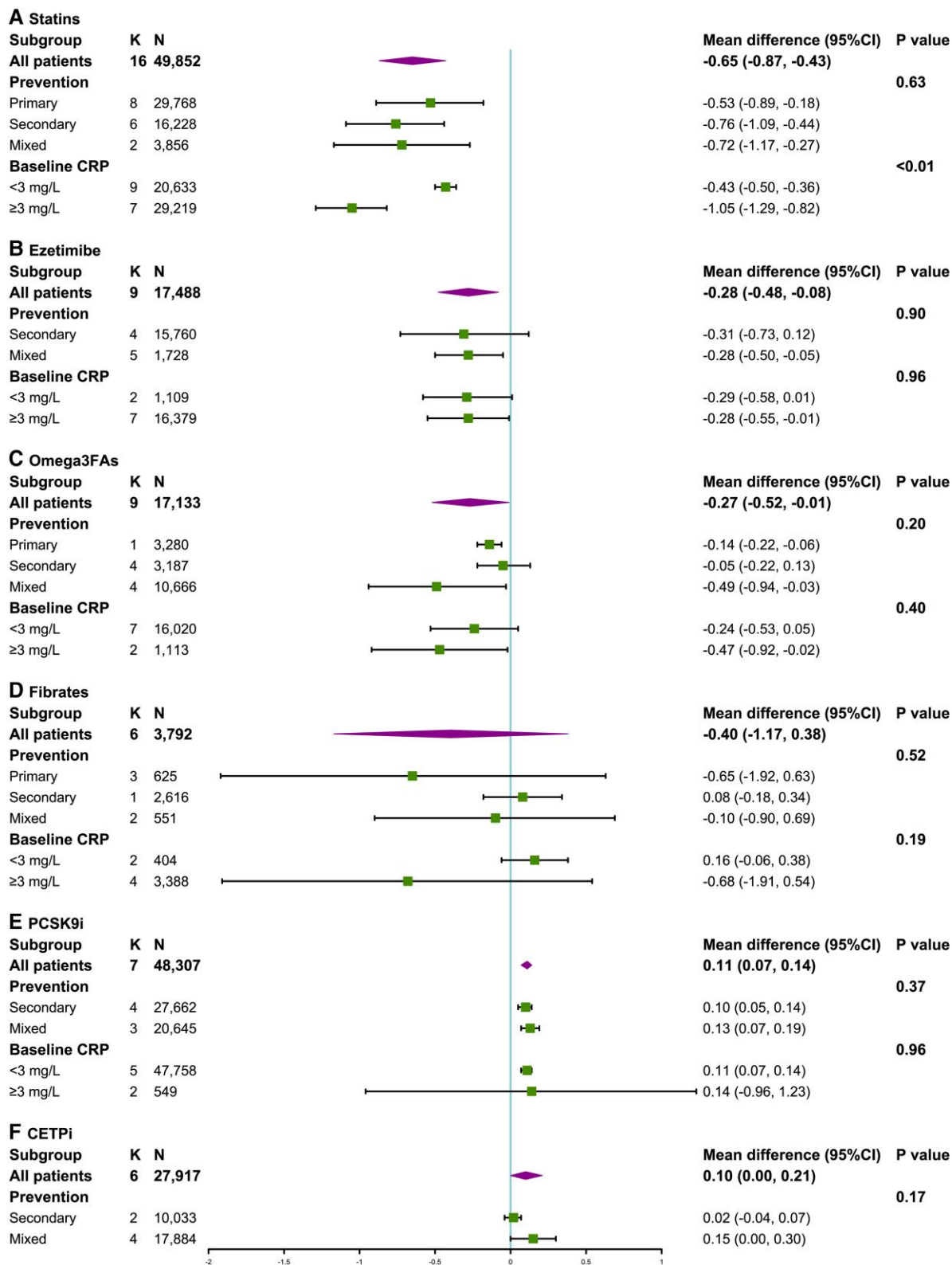


Figure 3 Forest plots illustrate the different changes in CRP levels among patients in primary CV prevention, secondary CV prevention, or mixed, and patients with low (<3 mg/L) or high (≥3 mg/L) CRP levels at baseline in each drug class. The results are shown in absolute change (mg/L). Only LLTs with more than one trial in at least two subgroups were subjected to subgroup analysis (bempedoic acid was not eligible). CETPi were not included in the subgroup analysis by baseline CRP levels as in all the trials patients had a baseline CRP <3 mg/L. CI, confidence interval; K, number of included trials; N, number of participants.

reduction. The results from our meta-analysis indicate statins, bempedoic acid, ezetimibe, and omega3FAs as the drugs with a significant impact on lowering CRP levels.

Statins thus emerge as the class with the largest anti-inflammatory effect, leading to an additional -0.65 mg/L absolute decrease of CRP concentrations (-17.31% from CRP value of ~ 3.75 mg/L at baseline in the 15 included trials) compared with the placebo group. The reduction was even more marked in the pooled analysis of trials with higher CRP levels at baseline. CRP levels in the MIRACL trial²⁰ including patients with acute coronary syndrome (ACS) were reported to be 11.25 mg/L at baseline and to have been reduced by 1.50 mg/L (-13.33%). However, we did not observe a significant change in our results after deleting this trial, according to the influence analysis (see [Supplementary material online, Figure S7](#)). Similarly, the CRP decreased by 1.18 mg/L from 4.47 mg/L at baseline when we combined the data from the JUPITER²¹ and CORONA(2)²² studies, which only included patients with baseline CRP of 2 mg/L or above. The result became -0.58 mg/L (-0.81 to -0.35) from 3.59 mg/L at baseline (-16.16%) after removing these two trials. This effect has already been suggested by a previously published meta-analysis,²³ in which the CRP reduction observed in the pooled analysis of statin-only trials was comparable. In the recent meta-analysis by Kandelouei *et al.*²⁴ on more than 40 studies, statins reduced the serum levels of CRP [-0.97 mg/L (95% CI -1.26 to -0.68)] in patients with CVD. This effect of statins has also been discussed to rely upon mechanisms beyond lipid control in CV prevention. The review by Lv *et al.*²⁵ reported that statins can attenuate disease activity markedly in patients with rheumatoid arthritis, with CRP declining significantly during the treatment. It was also suggested that the greater effect occurred in patients with higher baseline CRP levels. Horiuchi *et al.*²⁶ in 2010 showed that statin therapy reduced inflammatory markers in hypercholesterolaemic patients, with anti-inflammatory activity limited to subjects with elevated inflammatory markers at baseline.

Asher *et al.*²⁷ clearly illustrated that clinical trials with statins demonstrated a decrease in CRP levels of up to -43% ,²⁸ but the relative reductions in CRP levels appear to be independent of the magnitude of LDL-C lowering; indeed, statin trials that produced similar LDL-C reductions showed heterogeneous changes in CRP levels. Similarly, in our meta-regression, we failed to find an association between reductions in LDL-C and changes in CRP levels with this drug class.

Statins have been reported to exert *in vitro* properties that may contribute to a direct protective influence on the arterial wall *in vivo*,²⁹ and these pleiotropic properties appear to be derived from the inhibition of isoprenylation of the Rho kinase pathway.³⁰ Other hypothesized mechanisms for statin-mediated CRP reduction include a decrease in monocyte expression of inflammatory cytokines and in turn a downregulation of CRP gene transcription.³¹ An *in vivo* study provided evidence for a direct activating effect of statins of the peroxisome proliferator-activated receptor (PPAR α) and downstream suppressive effect on CRP gene expression independent of cholesterol lowering.³² Another *in vitro* study further demonstrated that statins could inhibit protein geranylgeranylation, reduce the IL-6-induced phosphorylation of signal transducer and activator of transcription 3 in hepatocytes, and eventually decrease CRP gene expression.³³

CRP levels were also reduced in response to bempedoic acid treatment, resulting in a -0.43 mg/L absolute decrease (-20.02% from baseline CRP value of ~ 2.15 mg/L) compared with the placebo. Our pooled results are consistent with a secondary biomarker analysis of the CLEAR harmony trial on patients with known atherosclerotic disease and residual inflammatory risk (defined as a baseline CRP ≥ 2 mg/L), showing a -26.5% (95% CI -34.8 to -18.4) reduction for CRP that was not correlated with bempedoic acid-associated lipid changes.³⁴ Bempedoic acid is a new hypolipidemic drug blocking the ATP citrate lyase enzyme, which in turn inhibits cholesterol synthesis through the same biosynthetic pathway as statins do. In addition, it targets the AMP-activated protein kinase pathway, resulting in strong anti-inflammatory effects proven by both *in vivo*^{35,36} and *in vitro*^{37,38} studies. In a previously published meta-analysis of seven RCTs, patients treated with bempedoic acid compared with placebo experienced a -13.2% (95% CI -16.7 to -9.79%) decrease in CRP levels.³⁹

The other drug showing a significant effect in CRP lowering was ezetimibe, with a -0.28 mg/L decrease in the ezetimibe-combined treatment

group compared with the single-statin treatment group (-3.19% reduction). It has to be acknowledged that the baseline CRP values in ezetimibe trials included in our analysis were much higher (~ 8.77 mg/L) than trials with other lipid-lowering drugs, and this was due to the inclusion of the IMPROVE-IT⁸ and HJ-PROPER⁴⁰ trials, the former on 18 144 patients stabilized after ACS (median CRP at randomization 10.2 mg/L, measured as mean of 5 days after presentation with ACS), and the latter on 1734 patients hospitalized for ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction or unstable angina within 72 h before randomization (median CRP at baseline 9.00 mg/L). Importantly, when we performed a sensitivity analysis omitting these two trials, the main results were confirmed [-0.26 mg/L (95% CI -0.47 to -0.04) with baseline CRP of 2.39 mg/L, -10.88%]. Combining these two trials, the CRP was reduced by -0.43 mg/L from 9.50 mg/L at baseline (-6.35%).

The pooled analyses by Pearson *et al.*⁴¹ (six trials on ezetimibe as monotherapy and seven trials as an add-on to baseline statin therapy), confirmed the reduction in CRP both by ezetimibe monotherapy (-6% from a baseline of 2.5 mg/L, $P = 0.09$) and when added to statin therapy (-10% from a baseline of 2.7 mg/L, $P < 0.001$). However, other studies showed that ezetimibe alone did not modify CRP.^{42,43}

The meta-analysis on omega3FAs also showed a considerable effect in reducing CRP levels [-0.27 mg/L (95% CI -0.52 to -0.01) compared with placebo]. For this drug class, there is a strong pre-clinical evidence base demonstrating the efficacy of omega3FAs for ameliorating inflammation and thereby reducing disease burden, but clinical trials have not provided compelling evidence that omega-3 supplementation reduces established inflammation.^{44,45} Recently, an umbrella meta-analysis⁴⁶ on 32 eligible meta-analyses conducted from 2012 to 2021 reported a significant effect [effect size: -0.40 (95% CI -0.56 to -0.24), $P < 0.001$].

Different mechanisms have been proposed for the possible impacts of *n*-3 polyunsaturated fatty acids (PUFAs) on inflammation:⁴⁷ *n*-3 PUFAs can affect innate and adaptive immune system responses,⁴⁸ act as the natural agonists of PPAR α ,⁴⁹ or replace arachidonic acid in the cell membrane.⁵⁰ Notably, in our analysis, this reduction was less evident [-0.13 mg/L (95% CI -0.19 to -0.06)] in the sensitivity analysis where the REDUCE-IT trial was excluded. REDUCE-IT⁵¹ randomly allocated 8179 statin-treated patients with triglyceride levels >135 and <500 mg/dL to treatment with 2 g twice daily of icosapent ethyl or a comparator (mineral oil). The levels of biomarkers associated with atherosclerosis increased over time among those allocated to the comparator ($+21.95\%$ for CRP at 12 months), while in the icosapent ethyl group, there were minimal changes (-1.03 mg/L). This led to the hypothesis that part of the net clinical benefit observed with icosapent ethyl might have been a consequence of adverse biomarker effects attributable to mineral oil. The result is smaller but still significant once we nulled the inflammatory effect of mineral oil (i) defining the CRP change in the placebo group as 0 [-0.18 mg/L (95% CI -0.29 to -0.06)]; (ii) considering the CRP change in the placebo group as the mean of changes in placebo arms across all omega3FA trials [-0.17 mg/L (95% CI -0.23 to -0.11)]; (iii) using the effect of corn oil in the STRENGTH trial⁵² as control value [-0.12 mg/L (95% CI -0.18 to -0.06)].

Our meta-analysis also showed that the effect of fibrates on CRP was limited as they showed an only marginal, nonsignificant reduction of CRP levels. The influence analysis highlighted that this reduction was mainly driven by the study by Zhu *et al.*, as excluding this trial in the influence analysis, the effect became null [0.00 mg/L (95% CI -0.21 to 0.22)]. In this trial, 594 enrolled patients with essential hypertension were randomized to 160 mg of micronized fenofibrate daily in combination with hypotensive agents or to hypotensive therapy alone. Treatment with micronized fenofibrate in combination with antihypertensive agents for 24 months showed a significant lipid-lowering and anti-inflammatory effect [CRP, mean (SD), from 6.73 (1.38) to 5.47 (1.09) mg/L]. In the meta-analysis by Hao *et al.*⁵³ on 16 RCTs, treatment with fibrates significantly decreased CRP concentrations [weighted mean difference: 0.47 mg/L (95% CI -0.93 to -0.01)]. The possible mechanism is under debate.⁵⁴ In patients with metabolic syndrome, fibrates were shown to reduce CRP independent of lipid-lowering

effects,⁵⁵ suggesting that PPAR α mediated the effect of fenofibrate could have a direct effect on the inflammation pathway. Evidence *in vivo* showed that changes in CRP with fenofibrate were significantly and inversely associated with changes in adiponectin.⁵⁶

PCSK9i and CETPi showed a slight or null effect on CRP levels, as already reported.^{57–59} Our findings were consistent with results from a recent meta-analysis⁶⁰ reporting that PCSK9i had no significant impact on circulating CRP levels irrespective of PCSK9-monoclonal antibody types, participant characteristics, and treatment duration. Interestingly, the analysis stratified by treatment also showed no differential effect with PCSK9i as monotherapy [0.00 mg/L (95% CI –0.08 to 0.07)] or combination therapy [–0.08 mg/L (95% CI –0.37 to 0.21)], with meta-regression confirming no significant linear correlation with LDL-C reduction. This effect, when compared with that of statins within the context of the two drug classes' ability to reduce LDL-C, aligns with the evidence found in the literature and is further confirmed by our meta-regression analysis. In other words, it underscores that the reduction of CRP is not correlated with the LDL-C reduction. It is worth noting, however, that the design of the included trials for these two treatments frequently containing a run-in phase with statin therapy, which is known to alleviate vascular inflammation. Taking this, both the low CRP levels at baseline and the lack of reduction in this biomarker after treatment could be partially explained, making further investigation necessary.

CRP is the classical acute-phase response protein, with its role in atherosclerotic plaque formation and progression of atherosclerosis is long debated.⁶¹ Although Mendelian randomization studies refuted the causal association between CRP and the risk of CV events,⁵ elevated CRP concentrations have been consistently associated with CVD,^{62,63} indicating that CRP may be rather a marker than a mediator of CVD risk. Even if CRP has demonstrated value as a predictor of CV risk, it remains yet unclear whether targeting CRP levels improves CV outcomes. The risk of CV events was significantly lower among individuals treated with colchicine (an anti-inflammatory drug) compared with placebo, according to the COLCOT⁶⁴ and LoCoDo2⁶⁵ trials. Canakinumab, a monoclonal antibody against IL-1 β evaluated in the trial CANTOS,⁶⁶ was shown to reduce the risk of secondary CV events, providing conclusive evidence that targeting the inflammatory processes of atherosclerosis alone improves CV outcomes. On the other hand, a recent meta-analysis on 15 RTCs that measured CRP before and after administration of therapies for CVD and measured incidence of CV events found that a greater magnitude of CRP reduction was not associated with better clinical outcomes, as improvements in clinical outcomes were largely accounted for by reduction in LDL-C.⁶⁷ Authors clearly stated that targeting CRP does not offer additional benefit over targeting LDL-C across the general population in terms of CV risk reduction, as confirmed by other studies in literature.^{68,69} However, there is value in targeting CRP in patients at high residual inflammatory risk despite non-elevated lipid levels.⁴ Indeed, a recently published study showed that among patients receiving statins, inflammation assessed by high-sensitivity CRP was a stronger predictor for risk of future CV events and death than LDL-C.⁷⁰ In September 2023, the use of low-dose (0.5 mg) colchicine had been approved in the US in patients with ASCVD. Meta-analyses illustrated that low-dose colchicine (0.5–1.0 mg) could reduce CRP by –0.36 mg/L [95% CI (–0.51 to –0.20)] in patients with CAD⁷¹ and by –0.66 mg/L [95% CI (–0.98 to –0.35)] in patients post MI,⁷² translating into a 35% [odds ratio 0.65 (95% CI 0.51–0.83)] and 44% [risk ratio 0.56 (95% CI 0.48–0.67)] reduction in major CV events, respectively.

5. Strengths and limitations

Our meta-analysis is a comprehensive and updated evaluation of seven main LLTs, counting 171 668 participants in a total of 53 trials. To the best of our knowledge, this is the first comprehensive meta-analysis to illustrate the absolute changes in CRP across several lipid-lowering drugs, including unpublished data, directly provided by authors. In addition, by converting absolute changes into percentage changes, we eliminated the

influence of the baseline values on the absolute changes and got a clearer picture of the extent to which the various LLTs have an impact on CRP reduction. However, some limitations exist. First, there were always some dropouts at follow-up, in this case, CRP and lipids may not have been measured for the same sample. Second, the small number of trials included for bempedoic acid and CETPi prevented conducting all the sub-analyses that could lead to more robust and reliable results. Third, we could not obtain the required data from authors of some RCTs reporting CRP levels (see [Supplementary material online, Table S8](#)), which may influence the results.

6. Conclusions

Among LLTs, statins, bempedoic acid, ezetimibe, and omega3FAs reduced serum CRP concentration, independently of LDL-C or TG changes. The CRP reduction seems to be greater in some specific groups of patients, mainly those with high CRP levels at baseline. While it is evident that the reduction in CV risk is primarily linked to the decrease in LDL-C levels, the existence of a remaining CV risk attributed to an underlying inflammatory condition could influence the selection of the hypolipidaemic therapy among those having an equivalent effect on LDL-C reduction.

Further investigation is required to clearly demonstrate how this potential anti-inflammatory action may influence CV protection, and whether new therapies targeting inflammation pathways (such as the recently approved colchicine) could be added to lipid treatment and used to help reduce CV risk in selected groups of individuals.

Supplementary material

[Supplementary material](#) is available at *Cardiovascular Research* online.

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Data availability

The data underlying this study are derived from *published articles* (available in the main text or in the supplementary materials), or *unpublished data directly provided by the authors* (this data will be shared on request to the corresponding author with permission of the original article's authors).

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