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REVIEW
Translational basic science

The role of inflammation and the possibilities of inflammation reduction to prevent cardiovascular events

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Chronic systemic inflammation is a risk factor for cardiovascular (CV) disease (CVD). Whether this relationship extends to subclinical inflammation, quantified by values of circulating markers associated with inflammation in the high range of the normal interval, remains debatable. This narrative review evaluates evidence exploring this relationship. A review of pharmacological and non-pharmacological interventions, including diet and lifestyle strategies, supplements, nutraceuticals, and other natural substances aimed at reducing inflammation was also conducted, since few reviews have synthesized this literature. PubMed and EMBASE were used to search the literature and several well-studied triggers of inflammation [oxidized LDL, Lp(a), as well as C-reactive protein (CRP)/high-sensitivity CRP (hs-CRP)] were included to increase sensitivity and address the lack of existing reviews summarizing their influence in the context of inflammation. All resulting references were assessed. Overall, there is good data supporting associations between circulating hs-CRP and CV outcomes. However, the same was not seen in studies evaluating triggers of inflammation, such as oxidized LDL or Lp(a). There is also insufficient evidence showing treatments to target inflammation and lead to reductions in hs-CRP result in improvements in CV outcomes, particularly in those with normal baseline levels of hs-CRP. Regarding pharmacological interventions, statins, bempedoic acid, and apabetalone significantly reduce circulating hs-CRP, unlike PCSK-9 inhibitors. A variety of natural substances and vitamins were also evaluated and none reduced hs-CRP. Regarding non-pharmacological interventions, weight loss was strongly associated with reductions in circulating hs-CRP, whereas various dietary interventions and exercise regimens were not, unless accompanied by weight loss.

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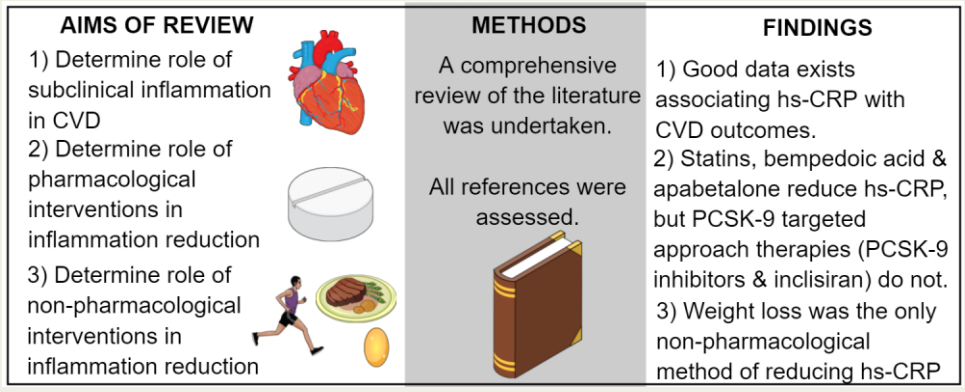
Graphical Abstract



Keywords Inflammation • hs-CRP • Cardiovascular disease

Introduction

Atherosclerosis is a complex process, which has been extensively studied in the past few decades. In 1998, Danesh *et al.*[1] conducted a large meta-analysis finding moderate, but highly significant, associations between markers of systemic inflammation and its intensity [namely fibrinogen, C-reactive protein (CRP), albumin, and leucocytes' count] and coronary heart disease (CHD). Since then, the relationship between cardiovascular (CV) disease (CVD) and low-grade systemic inflammation has been established, using more sensitive markers that indicate a mild subclinical inflammatory state, as well as molecules that may trigger the inflammatory process. One such molecule, lipoprotein a [Lp(a)], is a LDL-like particle, which contains apolipoprotein B100 bound to apolipoprotein(a) and has been modestly and independently associated with CHD and stroke by promoting a local inflammatory response and foam cell formation.[2,3] This association was also recently found to exceed that explained by its contribution as a form of cholesterol.[4] High-sensitivity CRP (hs-CRP), an acute phase reactant produced by the liver in response to acute systemic inflammation, has also been found to predict CV events[5] across many different countries and ethnicities,[6] and might do so better than LDL for first-time CV events.[7,8] Subclinical systemic inflammation assessed through hs-CRP has been found to predict CV events, and *in vivo* studies suggest CRP is associated with the formation of atherosclerotic plaques, although this data are controversial and further confirmatory research is required.[9,10] Localized inflammation in the sub-endothelial space (intima) leads to the production of oxidized LDL (oxLDL), the levels of which are significantly and positively associated with non-calcified plaque burden[11] and has been shown to be an independent risk factor in predicting acute CV events in healthy middle-aged men with moderate CHD risk.[12] Other mediators of inflammation have also been found to be implicated in CV disorders, such as myeloperoxidase[13] and the NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome.[14]

However, the focus of this paper will be on Lp(a), hs-CRP, and oxLDL. Although not markers of inflammation in the traditional sense, Lp(a) and oxLDL have both been shown to be triggers of systemic inflammation and could therefore be regarded as being pro-inflammatory indicators[15,16] and as CRP is produced in the liver as a result of interleukin 6 (Il-6) activity it can be regarded as being a biomarker which reflects the intensity of systemic inflammation.[17] Moreover, each has also been widely studied and can currently be used to help to predict CV risk in conjunction with other tools such as the Framingham risk score and other widely applied scores.[5]

The purpose of this study is to evaluate the role of inflammation in CV disease and to assess the evidence for pharmacological interventions together with non-pharmacological interventions, such as diet and lifestyle strategies and nutraceuticals and other natural supplements, aimed at reducing subclinical inflammation.

Role of inflammation

When considering patients with chronic inflammatory diseases, the evidence shows that they experience significantly higher rates of CVD events and mortality than the general population.[18]. However, it is now well accepted that patients who do not suffer from such diseases, but have subclinical elevations in blood inflammatory markers, are at an increased risk for CVD.[19–21] To estimate the size of this relationship, a large meta-analysis looked at the traditional markers of systemic inflammation, such as fibrinogen, CRP, albumin, and leucocyte count, and subsequent risk of developing CHD.[1] The authors found that when comparing individuals with baseline values in the top tertile to those in the bottom tertile, those in the top tertile displayed a risk ratio for developing CHD of 1.8 (95% confidence interval [CI], 1.6–2.0) for fibrinogen, 1.7 (95% CI, 1.4–2.1) for CRP, 1.5 (95% CI, 1.3–1.7) for albumin, and 1.4 (95% CI, 1.3–1.5) for leucocyte count.[1] In the case of CRP, the compared cut-off values used were 2.4 mg/L for the top tertile and 1.0 mg/L for the bottom

tertile.[1] Since the publication of this paper, tests to accurately detect lower levels of circulating CRP (denoted hs-CRP) have been developed to enable the accurate discrimination of normal values of CRP (often using a methodologically determined cut-off of under 3.0 mg/L, as defined by the Centres for Disease Control and Prevention and the American Heart Association (CDC/AHA)[22]) and the stratification of patients within an otherwise normal range of CRP.[23] One such cohort involved 3435 German males who were followed for an average of 6.6 years and evaluated for non-fatal and fatal cardiac events.[5] As compared with men with baseline hs-CRP values <1.0 mg/L, those with values between 1.0 and 3.0 mg/L displayed a hazard ratio (HR) of 1.73 (95% CI, 1.15–2.60) for developing cardiac events. For men with baseline CRP values above 3 mg/L, the HR rose to 2.91 (95% CI 1.98–4.29).[5] This study also found that CRP provides significant additive prognostic value for first-time cardiac events, to the Framingham risk score (FRS) for patients with a 10-year risk between 10 and 20%.[5] Another large cohort of 27 939 apparently healthy American women, followed for a mean of 8 years, looked not only at CRP, but also compared its predictive value to that of LDL-C for myocardial infarction (MI), ischaemic stroke, coronary revascularization, and death from CV causes.[7] They also looked at very low values of CRP, stratifying patients into quintile values of ≤0.49 mg/L, 0.50–1.08 mg/L, 1.09–2.09 mg/L, 2.10–4.19 mg/L, and >4.19 mg/L. After adjusting for traditional risk factors, those in the 2nd, 3rd, 4th, and 5th quintiles were at a relative risk of a first CV event of 1.4 (95% CI 0.9–2.2), 1.6 (1.1–2.4), 2.0 (1.3–3.0), and 2.3 (1.6–3.4), respectively, as compared with those in the lowest quintile.[7] Overall, the study found CRP to be a better predictor of CVD events than LDL and noted that values of these were only minimally correlated (r = 0.08). Based on these findings, the authors suggest that LDL and CRP can be used to define separate high-risk groups, even when the other is within normal limits.[7] This also points to the possibility that elevated cholesterol and inflammation may represent different pathways in the process of atherosclerosis. This notion is reinforced by the fact that while CRP is implicated in the modulation of LDL uptake by endothelial cells, it is also involved in many other steps of the atherogenic process.[20] Another paper looked at 6136 patients from the REGARDS study who had a Framingham risk score of ≥10% or atherosclerotic CVD risk ≥7.5% and compared patients with high and low hs-CRP as well as high and low LDL-C, and combinations of both. The authors found that while patients with high LDL-C ≥70 mg/dL and low hs-CRP (<2 mg/L) had a lower risk of incident stroke, incident CHD, and CHD death than patients with both high LDL-C and hs-CRP; finally those with low LDL-C (<70 mg/dL) but high hs-CRP (≥2 mg/L) did not see any significant reduction in these risks as compared with the high/high group.[24] This further reinforces hs-CRPs utility as a predictive factor in CVD. In another cohort that involved both men and women from the Nurses' Health Study and the Health Professionals Follow-up Study, the authors found a similar adjusted relative risk when comparing patients whose hs-CRP was >3.0 vs. <1.0 mg/L (relative risk = 1.68 (95% CI, 1.18–2.38),[24] but found CRP to be less associated with first CV events than plasma lipids. Interestingly, when looking at outcomes for patients who have already had a MI, one cohort evaluating the incidence of all-cause death, angina, and re-infarction at 6 months for 1371 MI patients did not find hs-CPR to be associated when adjusting for age, sex, and traditional risk factors.[25] However, Lp(a) and oxLDL were independently associated with a poorer prognosis for patients with blood values above 60 and 74 U/L, respectively, with HR of 1.40 (95% CI, 1.06–1.84) and 1.48 (95% CI, 1.06–2.06), respectively.[25]

Lp(a) has been shown *in vitro* and animal studies to promote inflammation and foam cell formation, with human data suggesting a clear relationship between the two.[26] However, this data may not be sufficient to use Lp(a) levels prognostically at this moment.[2,3] Furthermore, it is important to note that although Lp(a) is well-known to be responsible for inflammation in the arterial wall, it is perhaps better thought of as being a trigger of inflammation, rather than as an inflammatory biomarker in the traditional sense.[27] Despite this, Lp(a) concentration in the blood has been associated with an increased risk of CHD and stroke.[28] A systematic review and meta-analysis involving 126 634 participants across 36 prospective studies found that patients with a baseline Lp(a) of one standard deviation above the average (3.5-fold increase) had a risk ratio for developing CHD of 1.13 (95% CI, 1.09–1.18), and ischaemic stroke of 1.10 (95% CI, 1.02–1.18) after adjusting for age, sex, lipids, and other traditional risk factors. There was no relationship between Lp(a) and aggregate non-vascular mortality or cancer separately.[2] Another meta-analysis found a similar relationship, though noted large heterogeneity between studies. Further analysis revealed sample storage temperature to be most strongly correlated with this heterogeneity, citing issues with sample handling and standardization between studies.[3] A recent Danish study also found a significant relationship between Lp(a) and CV mortality, with a reported HR of 1.50 (95% CI, 1.28–1.76) when comparing people whose baseline values were above the 95th percentiles with those below the 50th percentile.[4] A similar relationship was seen with all-cause mortality with an HR of 1.20 (95% CI, 1.10–1.30).[4] What is notable is that this study compared this HR to those seen in patients with elevated LDL-C and found Lp(a) to be more strongly associated with both mortality measures than similar elevations in LDL-C, suggesting that the negative effects seen with Lp(a) are partially explained by phenomena outside of its cholesterol content.[4] In a study looking at 56 804 participants from 7 distinct populations the authors also observed a relationship between Lp(a) and CVD and major cardiac events, regardless of baseline LDL-C levels. However, no association was seen with total mortality, even when looking at patients with Lp(a) concentrations above the 90th percentiles.[29] Furthermore, several Mendelian randomization studies strongly suggest that the association between Lp(a) and CVD is causal and that much larger reductions in Lp(a) are required to achieve CVD risk reductions compared with LDL-C, again suggesting that the negative effects of Lp(a) particles are unlikely to be a consequence of their cholesterol content alone.[30–32] Despite this, unlike hs-CRP, there is also evidence that the relationship between Lp(a) and atherosclerotic CVD may not be universal. One study looking at 886 South Asians living in Americans did not find an association between blood Lp(a) concentration and the prevalence of coronary artery calcification, internal carotid artery intima-media thickness (IMT), or common carotid artery IMT, after adjusting for other CV risk factors.[33] However, whether a relationship exists between Lp(a) and CV mortality, directly, in this specific patient population is not known. Despite the strong association found in previous cohorts, this is an important finding, which should raise the question of generalizability when using

Lp(a) as a risk factor for future CVD. Of great interest is also the fact that while Lp(a) may be involved in promoting localized inflammation[2] and is clearly a risk factor for CV disease, it has not been found to be associated with the same low-grade inflammation responsible for CV disease as seen by elevations in hs-CRP, in an analysis involving 100 578 Danish individuals.[28,34] That said, there is evidence that Lp(a) particles can be susceptible to oxidative modifications which can render them pro-inflammatory and in this regard, although not being a direct marker of systemic inflammation, Lp(a) could be considered a contributing factor which is implicated in the inflammatory milieu.[35–37]

Oxidized LDL, similarly to Lp(a), is not typically regarded as being a biomarker of inflammation but has still been shown to trigger the condition and, unlike Lp(a), has been associated with both the progression and inhibition of inflammation. For example, regarding the latter, oxLDL has been shown to interact with and alter the oxylipid profiles of THP-1 macrophages which subsequently produce several anti-inflammatory prostaglandins and isoprostanes; a mechanism thought to alleviate cytotoxicity and inflammation.[38] However, the overall inflammatory balance appears to be shifted towards oxLDL being a source of vascular inflammation and atherogenesis,[39] with multiple pro-inflammatory mechanisms detailed, most of which implicate macrophage activity on and within endothelial cells.[38,40–42] When looking at the relationship between plasma oxLDL and CVD, a systematic review and meta-analysis of 12 studies found an effect size of 1.79 (95% CI, 1.56–2.05) when comparing cases of CHD and stroke with controls, and higher concentrations of circulating oxLDL to be associated with a greater likelihood of developing CHD and stroke.[43] However, the authors reported that only 7 of the 12 studies reached significance, and in particular, no association was seen for patients with rheumatoid arthritis and elderly community-dwelling patients.[43] This is the only such analysis that the authors are aware of and randomized control trials (RCTs) evaluating the effect on CV outcomes by changing blood levels of oxLDL are needed before a causal relationship can be established.

Does reducing inflammation provide a benefit?

Beyond the significant relationship between systemic inflammation and CV disease,[21] it is important to elucidate whether decreases in the above-mentioned aspects result in clinically significant reductions in incident CV events and CV mortality. Some drugs used in clinical practice can lead to reductions in levels of inflammatory markers as well as mortality, but their principal effects/uses make it difficult to separate these out. For example, statins are known to quell inflammation evaluated by reductions in circulating hs-CRP,[44,45] but their potent impact on blood lipids makes determining the mortality benefit of the hs-CRP reduction challenging. This is further complicated as hs-CRP only reflects levels of inflammation, rather than being an active participant and it is also unlikely to be a causal contributor to CVD.[46] Moreover, patients with systemic inflammatory diseases also experience significantly higher rates of CV morbidity and mortality than the general population.[47,48] A systematic review and meta-analysis that pooled patients with psoriasis, rheumatoid arthritis, and polyarthritis, found that treatment with methotrexate significantly reduced the incidence of total CV disease (21% risk reduction, 95% CI 0.73–0.87) and myocardial infarction (18% risk reduction, 95% CI 0.71–0.96) in this patient population.[49] However, in these patients, methotrexate reduces systemic inflammation. When tested in patients without autoimmune disease but with significant risk factors for heart disease (i.e. previous MI or multivessel heart disease), the CV Inflammation Reduction Trial (CIRT) found that treatment with low-dose methotrexate did not result in a reduction in either inflammatory markers or a composite endpoint of non-fatal MI, non-fatal stroke, or CV death.[50,51] However, it should be noted that patients recruited in the CIRT trial already had lower baseline hs-CRP values (medians of 1.53 and 1.50 mg/L for treatment and placebo arms, respectively) to begin with.[51] Also of consideration is that treatment of psoriasis patients with anti-inflammatory tumour necrosis factor-alpha (TNF-alfa) inhibitors has yielded conflicting results in this respect. In the retrospective cohort, the authors found a significant difference when comparing TNF-alfa inhibitors to topical therapy, but not to oral agents/phototherapy,[52] while a meta-analysis of RCTs of shorter follow-up did not find any association between TNF-alfa inhibitor administration and major adverse CV events (MACE),[53] though the authors suggest their study might be underpowered. Inhibition of interleukin-1ß by canakinumab in 10 061 patients with a history of MI and a baseline hs-CRP of 2 mg/L or greater [Canakinumab Anti-inflammatory Thrombosis Outcomes Study trial] led to both decreases in inflammatory markers and in non-fatal MI, non-fatal stroke, and CV death for patients given 150 mg canakinumab subcutaneously every 3 months as compared with placebo (HR 0.85; 95% CI, 0.74–0.98; $P = 0.021$).[54] The same was true for the composite secondary endpoint (including hospitalization for unstable angina leading to urgent revascularization) (HR 0.83; 95% CI, 0.73–0.95; $P = 0.005$).[54] However, of importance is that the treatment arms of 50 and 300 mg canakinumab did not reach statistical significance as compared with placebo. The pooled analysis of all doses found a benefit of the drug on CV disease, but the lacking dose–response relationship with 300 mg canakinumab could be concerning, and results should be revalidated by independent trials. What is more canakinumab was associated with a higher incidence of fatal infections and sepsis than was placebo; there was also no significant difference in all-cause mortality (HR 0.94; 95% CI, 0.83–1.06; $P = 0.31$).[50,55]

More direct evidence can be found in a major publication regarding 133 449 individuals with genetic copies of a variant of the IL-6 receptor (rs8192284; p.Asp358Ala). The findings revealed that each for allele present, there was an associated reduction of circulating CRP of 8.35% (95% CI 7.31–9.38) as well as an odds ratio of CHD of 0.95 (95% CI 0.93–0.97).[56] Moreover, a meta-analysis of clinical trials comparing 3–6-month administration of apabetalone to placebo found that apabetalone (RVX208) significantly decreased hs-CRP concentrations (−21.1%, $P = 0.04$) while decreasing MACE (5.4 vs. 12.5%, $P = 0.02$), an effect that was more pronounced in patients with higher baseline hs-CRP values.[57] The molecular targets of apabetalone are bromodomain and extra terminal domain (BET) proteins, and in particular the BET family member BRD4. Bromodomain and extra terminal domain proteins interact with acetylated lysines on histones bound to DNA to regulate gene transcription *via* an epigenetic mechanism. Apabetalone selectively binds to the second bromodomain (BD2). When apabetalone binds to

BRD4, it impacts key biological processes that contribute to CVD, such as cholesterol levels (by stimulating ApoA-I gene expression) and inflammation.[58] Thus, apabetalone also increased apolipoprotein A-I (6.7%, $P < 0.001$), HDL-C (6.5%, $P < 0.001$), and large HDL particles (23.3%, $P < 0.001$) over the same period, but without decreasing atherogenic lipids.[57]

Evidence from the JUPITER (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) and CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trials is possibly more telling, with clear total mortality and coronary events benefits for patients taking rosuvastatin and having high baseline hs-CRP. However, the same cannot be said of patients with low (<2.0 mg/L) baseline hs-CRP concentrations, though this could be explained by the fact that rosuvastatin only decreased hs-CRP by 6% in the low-concentration group, while decreasing it by 33% in the high-concentration group.[59] Ridker[59] further suggests that these benefits are independent of the impact of rosuvastatin upon LDL-C, as LDL-C and hs-CRP were not well correlated in the above studies. Looking at data from the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trial evaluating lovastatin, CV event rates were reduced in patients with lower baseline LDL-C values and high hs-CRP values, but not in patients with the same LDL-C concentrations and low baseline hs-CRP values despite an improvement in lipid profiles.[60]

With respect to the inflammatory trigger lipoprotein(a), similar evidence is missing. Saeed and Virani correctly point out that in the case of nicotinic acid (niacin), its use can lower circulating Lp(a) by more than a third. Yet patients with CVD enrolled in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) and HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) trials did not see a mortality benefit from its administration.[61] *Post hoc* analysis of the former found that Lp(a) levels at baseline and during the study were predictive of CV events in all groups. However, despite the extended-release niacin treatment group seeing a 21% reduction in Lp(a), the rate of CV events was not lower.[62] Admittedly, many factors could confound these results, including that all patients were already treated with simvastatin at baseline. Also, it is possible that only treating those with very high circulating levels of Lp(a) results in a reduction of CV events. Other drugs currently under investigation are antisense oligonucleotide inhibitors of apo(a) (pelacarsen), PCSK9 inhibitors, and inclisiran (small interference RNA), which have been shown to significantly reduce Lp(a).[63,64] However, trials evaluating whether this reduction in circulating Lp(a) leads to a reduction in incident CV disease and/or mortality are needed to elucidate the impact of Lp(a) targeted therapy.[63]

Similarly, despite the heavily documented associations between the inflammatory trigger oxLDL and CV disease and mortality, trials assessing whether reducing circulating oxLDL improves outcomes are currently lacking. One study evaluating data regarding patients using haemodialysis treated with rosuvastatin or placebo found no improvement in MACE or all-cause mortality despite an overall 20.4% decrease in circulating oxLDL at 12 months for patients in the treatment arm.[65] Though this may be explained, as Gao and Liu[66] suggest, by the fact that oxLDL may promote atherosclerosis at different points in its lifecycle meaning much longer reduction durations are needed before a benefit can be detected. Furthermore, the atherosclerotic burden of patients on haemodialysis is very high, along with extensive vascular calcification. In this setting, reducing systemic inflammation and/or lipids may not be as impactful. This is evidenced by the fact that statins also have not been shown to reduce CV mortality in patients on haemodialysis.[65] As such, larger trials specifically targeting oxLDL, in a more general population, and with longer follow-ups, are necessary.

Evidence of pharmacological and non-pharmacological therapeutics

Given the strong associations between systemic inflammation and CVD, much research has looked at whether pharmacological interventions can lower markers including hs-CRP, and other associated triggers such as Lp(a), and oxLDL, and whether non-pharmacological approaches, such as lifestyle modifications, exercise, and natural substances can have a beneficial impact. This section briefly explores the current evidence for the most well-studied of these approaches.

Pharmacological

- *Statins* have been known for almost two decades to reduce circulating CRP.[67] The largest trial evaluating related outcomes is the 2008 JUPITER trial, which compared 20 mg daily of rosuvastatin with placebo in apparently healthy patients without hyperlipidaemia (defined as LDL-C < 130 mg/dL) but with elevated hs-CRP (2.0 mg/L or greater) in order to isolate the impact of a reduction in subclinical inflammation on CV outcomes.[68] Patients in the treatment group experienced a 37% decrease in circulating hs-CRP and a 50% decrease in LDL-C but saw a reduction in first-time CV events that was twice as great as would be expected by such a drop in LDL-C alone.[68] However, it is important to note that statins have pleiotropic effects which impact upon CVD via a multitude of mechanisms from atheromatous plaque stabilization to increasing local nitric oxide (NO) production and vasodilation.[69,70] Each contributes to CV health, but their individual contributions are difficult to quantify.[69] As such, it is difficult to ascertain the exact contribution to CV health given by the reduction in systemic inflammation in patients treated with statins. That is not to say, however, that the finding was insignificant; the 2013 ACC/AHA (American College of Cardiology/AHA) guidelines for the assessment of CV risk based on their recommendation that hs-CRP be used as an indicator to initiate statin treatment if traditional indicators were inconclusive, largely on the JUPITER trial.[71,72] Another trial performed on patients with documented CAD, randomly assigned to a moderately intense statin regimen (pravastatin 40 mg daily) or a high-intensity statin regimen (atorvastatin 80 mg daily), found that regimen intensity was associated with reductions in CRP, and that CRP reduction magnitude was significantly associated with the level of decrease in the rate of progression of atherosclerotic plaques, as measured by intravascular ultrasonography.[73] This concept also translates to patient outcomes. In other trials comparing the same drugs and doses as those aforementioned, the authors evaluated 3745 patients with acute coronary syndromes for their risks of recurrent MI or death from coronary disease.

In patients with a CRP above 2 mg/L after treatment, the rate of MI recurrence was 4.6 per 100 person-years (PY). Meanwhile, those with CRP under 2 mg/L had a rate of MI recurrence of 3.2 per 100 PY, while patients with the lowest levels (under 1 mg/L) saw rates of recurrence of only 1.9 per 100 PY ($P < 0.001$ for all).[74] Another study reinforces the importance of hs-CRP reduction by looking at the long-term survival of patients presenting with non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction and evaluating their relationship to hs-CRP measured at 30 days and 4 months after initial presentation. After controlling for traditional risk factors, they found that patients with hs-CRP > 3 mg/L at 30-days saw a significantly higher 2-year mortality than those with hs-CRP 1–3 mg/L or those with hs-CRP < 1 mg/L (6.1 vs. 3.7 vs. 1.6%, respectively, $P < 0.0001$).[75] Similar associations were seen for hs-CRP measured at 4 months.[75] The impact of statins on oxLDL has been presented above. Interestingly, although statins may increase levels of Lp(a) by 6–7%, this has no clinical relevance [besides pitavastatin, which might even reduce Lp(a) by 6.4 mg/dL[76]], thus in those with elevated levels of Lp(a), combination therapy with ezetimibe is recommended.[77]

- *Ezetimibe* has not been considered as an agent to reduce inflammation, however, there are inconsistent data suggesting its role. When added to rosuvastatin, has been shown in one trial to reduce hs-CRP by more than rosuvastatin in monotherapy (5.15–0.68 vs. 4.33–1.49 mg/L, $P < 0.05$) in patients suffering from acute myocardial infarction.[78] Another trial comparing ezetimibe plus atorvastatin vs. atorvastatin alone found ezetimibe to significantly reduce circulating oxLDL, but that this was through a decrease in total LDL-C and large buoyant fractions alone.[79] When comparing the same drugs, but double-dose atorvastatin vs. normal-dose atorvastatin plus ezetimibe, the RCT did not find differences in oxLDL or hs-CRP between the two groups,[44] suggesting that perhaps atorvastatin and ezetimibe exert similar effects on circulating oxLDL and hs-CRP, especially when taking the previously mentioned data into account. A large trial of 18 144 patients stabilized post-MI were randomized to either 40 mg simvastatin plus placebo or 40 mg simvastatin plus 10 mg ezetimibe to evaluate the impact of achieving either LCL-C < 70 mg/dL and/or hs-CRP < 2 mg/L, or neither, on CV death, MACE, or stroke. The authors found that when patients achieve both targets, rates of the primary endpoint were similar between groups.[80] This suggests that in statin-intolerant patients, achieving LDL-C and hs-CRP targets with ezetimibe (or other medications, though this remains to be elucidated) may be a good option. Another study evaluating weight loss alone or in combination with ezetimibe found the latter to decrease both hs-CRP and IL-6 by −53 and −24%, respectively, as compared with weight loss alone ($P < 0.05$ for all).[81] However, current evidence suggests that ezetimibe alone only exerts a modest effect on non-fatal MI and non-fatal stroke (mainly due to modest impact on LDL-C with reduction only by 15–20%) and has almost no impact on CV or all-cause mortality,[82] though cited studies did not evaluate for baseline hs-CRP, nor changes in this parameter. As such, it is possible for ezetimibe alone to exert positive effects on CV mortality through a reduction in hs-CRP in certain patient populations (namely, those with elevated baseline hs-CRP), and should be investigated. There are also some data suggesting a modest reduction in Lp(a) with ezetimibe monotherapy.[83] If this relationship is confirmed, there may exist an indication for combination therapy in patients who are already on a statin but have persistently elevated Lp(a) level.
- *Bempedoic acid* (a.k.a. ETC-1002) is a new drug under development produced with the intention of treating hyperlipidaemia that has been already approved in February 2020 by the Food and Drug Administration (FDA) and in April 2020 by the European Medicines Agency (EMA). Bempedoic acid is a prodrug that is activated to the thioester with coenzyme A by the enzyme SLC27A2 in the liver. The activated substance inhibits ATP citrate lyase, which is involved in the liver's biosynthesis of cholesterol upstream of HMG-CoA reductase.[84] It has also been found to significantly reduces circulating hs-CRP. When added to ezetimibe, one RCT found it to reduce circulating hs-CRP by 31.0% ($P < 0.001$) when compared with ezetimibe alone.[85] In a smaller trial of participants with Type 2 diabetes mellitus, bempedoic acid reduced circulating hs-CRP by a median of 41% compared with an 11% reduction seen in patients given placebo ($P = 0.001$).[86] Another trial with parallel treatment arms assigned to different doses of bempedoic acid (120 vs. 180 mg) found decreases in hs-CRP to be similar to previous studies, but also a dose-dependent effect between the two groups (reductions of 30.1 and 40.2% from baseline, for 120 and 180 mg, respectively).[87,88] In the CLEAR Harmony trial at Week 12, bempedoic acid at the dose of 180 mg reduced the mean LDL cholesterol level by 19.2 mg/dL, representing a change of −16.5% from baseline (difference vs. placebo in change from baseline −18.1%; $P < 0.001$). The difference in the changes in the level of hs-CRP at Week 12 was –21.5% (95% CI, –27.0 to –16.0; $P < 0.001$); results were consistent in the on-treatment analysis. In the pooled analyses of Phase 3 trials and in the meta-analysis of Phase 2 and Phase 3 trials, bempedoic acid was confirmed to significantly reduce LDL-C by 17.8% (placebo corrected; 24.5% in statin-intolerant patients), and 22.94%, respectively, and hs-CRP by 18.1% (27.4% in statin-intolerant patients), and 27.03%, respectively.[89,90] Safety and efficacy findings were consistent, regardless of the intensity of background statin therapy.[91] As far as the authors are aware, no studies powered for morbidity and mortality have been completed thus far (it is necessary to wait for the CLEAR-OUTCOMES trial results), and so it is difficult to say what impact bempedoic acid might have on these.
- *Apabetalone* (a.k.a. RVX-208 and RVX000222), as previously mentioned, is an inhibitor of BET proteins, which function in the transcription of DNA to mRNA.[92] In a pooled analysis of patients from the ASSERT (ApoA1 Synthesis Stimulation Evaluation in Patients Requiring Treatment for Coronary Artery Disease), ASSURE (ApoA-I Synthesis Stimulation in Acute Coronary Syndrome patients), and SUSTAIN (Study of Quantitative Serial Trends in Lipids with Apolipoprotein A-I Stimulation) trials, patients treated apabetalone for a duration of 3–6 months saw hs-CRP reductions of 21.1% ($P = 0.04$).[57] Compared with placebo, patients given apabetalone also saw fewer MACE (5.9 vs. 10.4%, $P = 0.02$) overall, with a larger impact in patients with diabetes, lower baseline HDL-c values, and higher baseline hs-CRP values.[57] This same analysis found that while apabetalone did not affect atherogenic lipid profiles as compared with placebo, it did lead to significant increases in apoA-I, HDL-C, and large HDL particles (6.7, 6.5, and 23.3%, respectively, $P < 0.001$ for all).[57] However, it is important to note that these trials were not adequately powered to detect differences in mortality between those treated with apabetalone vs. placebo, and more data are required before the degree to which this drug can reduce CV mortality can be fully understood and how much of this is contributed to by reductions in hs-CRP.

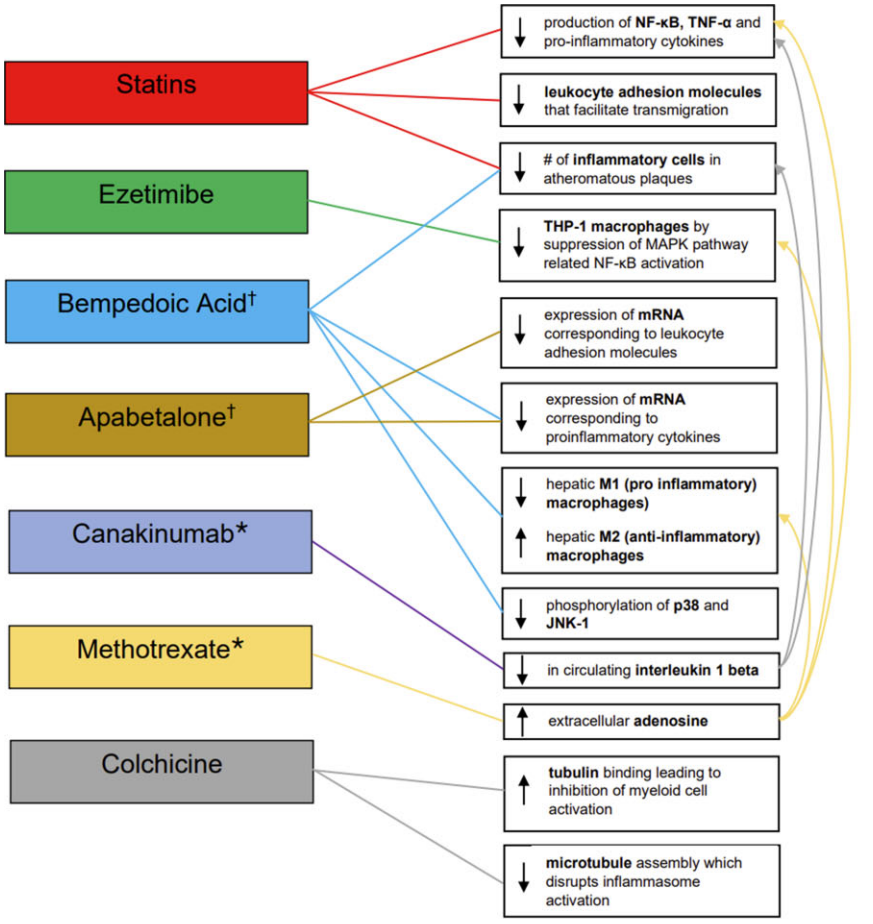
- *PCSK9 inhibitors* (alirocumab and evolocumab) Regarding the newer PCSK9 inhibitors, meta-analyses on RCTs have not found these drugs to impact circulating hs-CRP concentration,[86,87] but they have been shown to further reduce LDL-C and mortality when added to statins,[93] an effect that was stronger for patients with higher baseline hs-CRP (>3 mg/L).[94] It is also worth mentioning that there is accumulating evidence showing lessened inflammatory response in the arterial wall that could attenuate atherosclerotic plaque development beyond the established LDL-lowering effect of PCSK9 inhibition.[95] Additionally, significant reduction of Lp(a) with PCSK9 inhibitors by even 30% might also play a role in the inflammation reduction, independently on the LDL-C levels.[96] When discussing PCSK9 inhibitors, it is critically important to mention the already approved small interference RNA molecule called inclisiran, which also inhibits the PCSK9 protein by mRNA catalytic degradation. Based on the Phase 3 trials data, inclisiran also significantly reduce lipoprotein(a) by up to 30%.[97]
- *Colchicine* Is a potent anti-inflammatory medication previously used to treat gout and pericarditis and has reemerged as an add-on therapy for secondary prevention of coronary events. Its mechanisms are complex and pleiotropic, primarily acting to interfere microtubule assembly in T lymphocytes, hampering their ability to become active in the presence of an antigen.[98] This is based on results of the COLCOT Trial looking at patients who have suffered a recent myocardial infarction,[99] with additional evidence of benefit in patients with chronic coronary disease as seen in the LoDoCo2 trial.[100] The rationale behind these trials involves previous evidence associating atherosclerosis and systemic inflammation, much of which is detailed above. A recent systemic review and meta-analysis pooling data from 12 RCTs, similarly shows a lower risk of MACE, recurrent MI, and hospitalization due to CV events, but overall similar all-cause and CV mortality.[101] Based on these results, in the recent ESC Prevention Guidelines (2021), colchicine was indicated as a drug to reduce inflammation and a low dose (0.5 mg once daily) should be considered for the secondary prevention of CV disease, especially in high-risk patients.[102] *Figure 1* details the presumed mechanisms by which the aforementioned medications act to reduce systemic inflammation, and local inflammation within atheromatous plaques. Please note that some of these are based on limited data and require more research to be confirmed. As a detailed discussion on the molecular functions of the biology underlying these mechanisms of action is beyond the scope of this paper, the authors encourage you to consult the references added to the figure for further reading.

Non-pharmacological

Diet and lifestyle modifications

The relationship between systemic inflammation and weight, diet, and exercise, has been studied extensively in recent years, and the benefits of these are perhaps unsurprising. One study of Korean adults has found strong correlations between circulating hs-CRP and anthropometric measures such as body mass index (BMI) ($r = 0.525$, $P < 0.0001$), waist circumference ($r = 0.507$, $P < 0.0001$), waist-to-hip ratio ($r = 0.436$, $P < 0.0001$), and visceral fat ($r = 0.558$, $P < 0.0001$).[103] The authors also found that even among patients with low levels of hs-CRP (<1 mg/L), those with level <0.5 mg/L had significantly better anthropometric measures than those with circulating levels between 0.5 and 1.0 mg/L.[103] These findings have been replicated in other papers,[104] and visceral adiposity has been found to be significantly correlated with hs-CRP concentration even after controlling for BMI and waist circumference (WC).[104] As a testament to this association, weight loss has been shown to significantly reduce hs-CRP in overweight[105] and obese[105,106] adults, as well as obese children and adolescents.[107]

Multiple diets have also been previously investigated. A high-protein diet, meal replacement programme, with or without alternate day fasting, has been found to reduce hs-CRP and also support weight loss.[108,109] Another study, however, found that a high-protein diet without weight loss did not see any improvement in circulating hs-CRP.[110] Another RCT, looking at obese women at risk for metabolic syndrome, compared a Central European Diet with a Mediterranean Diet, and found both to significantly reduce circulating hs-CRP levels overall, but not between themselves.[111] It is important to note that subjects in both interventional arms also experienced significant weight loss, which could be an important confounder. Another RCT that compared calorie and saturated fat-restricted diets with high vs. low egg intake, in patients with prediabetes or Type 2 diabetes mellitus, also found an overall decrease in inflammatory markers from baseline, but not between groups.[112] Finally, the POUNDS LOST (Preventing Overweight Using Novel Dietary Strategies) trial, which enrolled 710 participants randomized to four diets of different macronutrient distributions for 24 months, found significant decreases in hs-CRP in all groups, but no difference between groups.[113] The only study the authors are aware of where a dietary modification led to a significant difference in markers of inflammation, after controlling for BMI and WC, compared a vegan diet to the diet prescribed by the AHA. This trial involving 100 randomized participants found that subjects eating a vegan diet saw 32% lower hs-CRP ($P = 0.02$) levels than those eating the AHA diet, after adjusting for age, race, baseline WC, DM, or previous MI,[114] although the findings were likely limited by sample size. More recently, a systematic review and meta-analysis were performed which compared vegetarian and vegan diets to a placebo diet (described as 'omnivore'), with respect to a multitude of inflammatory biomarkers.[115] They did find a statistically significant difference in CRP between vegan and omnivore diets [weighted mean difference (WMD) = −0.54, 95% CI −0.79 to −0.28], but this is based on the inclusion of only three studies again totalling only 266 subjects. Studies comparing vegetarian to omnivore diets were greater in number and subjects ($n = 7099$ subjects), and pooled analysis showed a modest reduction in hs-CRP in the former, although its significance is questionable as the confidence interval includes zero (WMD −0.25, 95% CI −0.49 to 0.00).[115] It is important to note that when looking at the treatment arms of all the included studies individually, sometimes large differences in body mass and composition are seen. For vegan diets, the only study of the three to show a significant difference in hs-CRP also suffers from 'BMI Bias', as subjects in the vegan treatment arm of the also had significantly lower BMI and WC as compared with those in the omnivore (placebo) arms (BMI 23.2 vs. 26.4, $P < 0.001$; WC 79.7 vs. 86.5 cm, $P = 0.001$). For the vegetarian analysis, five individual studies found a statistically significant decrease in hs-CRP as compared with omnivore diets, and two an increase. In all the former, participants eating omnivore diets had significantly higher BMIs and WC than those eating vegetarian ones, while in the latter BMI and WC were not different between groups. Exploring the relationship



Glossary: JNK-1 = c.Jun N-terminal kinase 1, NF-κB = nuclear factor kappa-light -chain-enhancer of activated B cells, TNF-α = tumor necrosis factor alpha.

† - Drugs are still in production and currently commercially available.
★- Not currently approved for cardiovascular prevention.

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Figure 1 Assumed mechanisms of action by which these drugs reduce systemic and local inflammation. Please note that some of these are based on limited data and therefore not conclusive. Moreover, this list is not exhaustive as more research is underway.

between diet and inflammation through the opposite lens, a large cross-sectional analysis of 1758 British adults enrolled in the UK National Diet and Nutrition Survey examined red meat and processed red meat consumption.[116] The study stratified men and women into terciles of consumption of red meat and processed red meat, measured in grams per day, which roughly corresponds to <20, 20–50, and 50–150 g/day, respectively. There was no significant difference in CRP for either gender in any tercile of consumption of either red meat or processed red meat. Ferritin was significantly higher for men consuming processed red meat in the middle as compared with the lowest tercile (153 μg/L vs. 101 g/L, $P < 0.001$); however, this association is not dose responsive as men in the highest tercile of consumption saw only modest elevations in the blood ferritin as compared with the lowest tercile, but lower than those in the middle tercile (127 μg/L, $P < 0.001$).[116] Lastly, looking at overall nutrition, one meta-analysis examining the relationship between dietary

nutrient intake and hs-CRP in 17 689 participants found small, but statistically significant differences in intake of total polyunsaturated fatty acids, dietary fibre, vitamins E, A, B2, B3, B6, B9, total B vitamins, C, K, magnesium, iron, copper, and potassium, across all quartiles of circulating hs-CRP values.[117] More expected was the large difference in BMI and WC between the top and lowest quartiles of hs-CRP values at 33.1 ± 0.1 vs. 24.6 ± 0.08 ($P < 0.001$) for BMI, and 107.7 ± 0.4 vs. 87.7 ± 0.2 cm for WC, validating previous research.[117] Overall, almost all studies that demonstrate a difference in hs-CRP between diets (or a diet and placebo) also see a significantly lower BMI and/or WC in the group with the lower hs-CRP, and this makes the results very difficult to interpret. In conclusion, it is highly likely that weight loss, and not the specific diet chosen to achieve this goal, is most important in achieving lower circulating hs-CRP levels. There is a lack of evidence of an impact on systemic inflammation from dietary modification alone.

Data on the association between exercise and systemic inflammation are less clear. One meta-analysis of five studies evaluating aerobic exercise in healthy subjects found significant decreases in hs-CRP related to weight loss and body fat composition, but not to exercise independently.[118] Another meta-analysis of 43 studies comparing healthy adults to those with pre-existing CHD found that both groups experienced a significant decrease in hs-CRP when undergoing aerobic or mixed exercise routines, but no difference between healthy and CHD groups.[119] However, weight loss in study participants does not seem to have been controlled for in the analysis, which may account for the decrease in hs-CRP observed. Another trial of 464 overweight and hypertensive post-menopausal women assigned to 6 months of aerobic training (three groups of different intensities, and a control group without any exercises). There was no significant difference in hs-CRP between the exercise groups and control group except in the case where subjects also lost weight.[120] A smaller trial of healthy adults undergoing strength training also did not see changes in hs-CRP or fibrinogen at 5 weeks of training,[121] though the group size was small ($n = 18$) and compared regular resistance training to training under conditions of blood flow restriction. Lastly, a study comparing young healthy male athletes to non-athletes that did not undergo regular exercise found that the athletes has significantly higher, not lower, circulating hs-CRP than the non-athletes (3.52 ± 0.23 vs. 2.40 ± 0.37 mg/L, $P = 0.003$).[122] The authors explain that this could be due to higher incidence of physical stress seen in athletes. Moreover, they did not find any significant differences in circulating markers of oxidative stress between the two groups, namely asymmetric dimethylarginine, symmetric dimethylarginine, or L-arginine.[122] Overall, evidence showing a decrease in hs-CRP in subjects who exercise is inconclusive, or improvement is seen only in the setting of weight loss. The authors could not find sufficient evidence that exercise of any category (e.g. aerobic, strength training, intense athletic performance) by itself is associated with circulating hs-CRP.[123,124]

Natural substances and supplements

As patients are increasingly using natural substances and supplements for their perceived health benefits, the authors feel it is important to evaluate the existing evidence for their use in reducing systemic inflammation.[125,126] It is worth emphasizing that recently the International Lipid Expert Panel (ILEP) for the first time evaluated the available data to investigate the potential effect of nutraceuticals on inflammatory markers.[127] The authors summarize their recommendations in Table 3 of their Position Paper, and this is additionally presented in Supplementary material online, *Table S1* for reference (express consent for reproduction has been given by the authors and copyright holders).[127] For the purposes of this paper, and considering the increasing interest in natural products, further information is also presented in *Table 1*.

- *Spirulina platensis* is a blue-green algae derivative that has been studied for a wide variety of health claims. One RCT compared 2 g of spirulina tablets daily plus a calorie-restricted diet vs. calorie-restricted diet alone for 12 weeks in 52 obese and overweight subjects, of which 38 completed the trial. They saw a significant reduction in the treatment group's hs-CRP vs. placebo, however, the treatment group also saw a significant reduction in weight and BMI, whereas the placebo group did not experience the same loss.[128] As discussed previously, weight loss is a significant confounder for hs-CRP reduction, and an RCT administering spirulina vs. placebo alone (i.e. without diet) is necessary before a clear relationship can be established.
- *Coenzyme Q10* has been investigated as well, and one RCT compared CoQ10 plus selenium vs. placebo administration for 48 months in 443 patients, who were subsequently followed-up for a median of 5.2 years for total mortality. By the end of the 48 months, CRP concentration in the treatment arm significantly decreased from 4.06 ± 11.7 to 2.07 ± 2.3 mg/L (mean ± SD), whereas the placebo group saw a small increase in CRP.[129] At the end of follow-up, the cumulative proportional surviving for the treatment arm was 0.92, whereas this was just above 0.87 in the placebo group, a difference that was significant ($P = 0.021$). Like with spirulina, however, the authors did not also account for baseline and end-of-study weight, BMI, or WC. Furthermore, patients in the placebo arm were significantly more likely to be taking angiotensin-converting enzyme inhibitors (14.8 vs. 24.0%, $P = 0.02$), while not being statistically different with respect to any other class of medications. This may mean they were experiencing poorer health at baseline. Moreover, a meta-analysis of seven studies looking at CoQ10 administration alone (i.e. without selenium) did not find a statistically significant decrease in hs-CRP.[130] However, a systematic review and meta-analysis of 16 RCTs evaluating selenium administration in patients with CHD did find significant decreases in serum CRP concentrations, but it is important to note that this decrease did not result in an improved mortality benefit.[131]
- *Tomatoes and lycopene* (a carotenoid found in red fruits and vegetables) were also evaluated, and one meta-analysis of 21 RCTs found significant reductions in Il-6 for patients given tomato products [standardized mean difference (SMD) −0.25; $P = 0.03$].[132]
- *Zinc* supplementation was investigated through a meta-analysis of eight RCTs, which found a significant overall decrease in circulating CRP (WMD = −1.68 mg/L, 95% CI −2.4 to −0.9, $P < 0.001$). However, as the authors correctly discussed, the studies were very heterogeneous, with significant differences in baseline patient characteristics between studies, among other factors.[133] More high-quality research is necessary before a link with zinc can be established.
- *Magnesium* supplementation was assessed by a meta-analysis of eight RCTs, indicating a significant reduction in serum CRP concentrations following magnesium supplementation (WMD −1.33 mg/L; 95% CI: −2.63 to −0.02) without significant effect on IL-6 (WMD = −0.16 pg/dL, 95%

Table 1 Studies evaluating the effects of different supplements on serum CRP.

Supplement	Study type + duration	Participant characteristcs	# of participants	Results
Spirulina platensis[128]	RCT—12 week duration	Obese adults with an average age of ~40 ± 9 years	52 enlisted. 38 completed trial. Female% = 77.4%	Spirulina group saw a significant decrease in hs-CRP at 12 weeks (5.09 ± 3.94) vs. baseline (6.18 ± 2.9) and placebo at 12 weeks (6.93 ± 3.7), $P < 0.05$ for all. Data possibly confounded by significant weight loss in the intervention group.
Coenzyme Q10 + selenium[129]	Secondary analysis of RCT—48 month duration with 5.2 year average follow-up	Elderly individuals with an average age of ~77 ± 3.4 years	437 participants. Female% = 49.2%	Treatment group saw a decrease in CRP from baseline to 48 months (4.1 vs. 2.1 ng/mL), but was not significant ($P = 0.08$). Placebo arm saw increase in CRP over study period. Treatment group saw decrease in CV mortality at follow-up, but this was only significant for those with baseline CRP below the median concentration.
Coenzyme Q10[130]	Meta-analysis of seven RCTs—8–12 week duration	Diverse. Mean ages in studies range from 41.3 to 79.9 across both placebo and treatment groups.	226 test and 159 control participants across all studies. Female% ranges from 0 to 87% across studies.	Pooled CoQ10 supplementation resulted in a small, but non-significant decrease in blood CRP concentration (−0.25 mg/L, 95% CI −0.56 to 0.06, $P < 0.001$). Looking only at studies where dosage given was 200 mg/day or greater, blood CRP concentrations decreased by −0.32 mg/L (95% CI −0.61 to −0.07, $P < 0.001$).
Selenium[131]	Meta-analysis of four RCTs[a] with respect to CRP measurements —treatment duration ranged from 8 weeks to 5.2 years.	Diverse. Mean ages in studies range from 62 to 78 years, with one study only listing age range as 40–85. Female% ranges from 18 to 66%.	Total of 43 998 participants across 16 studies. Mean female% is 42.75% across studies.	Selenium supplementation decreased serum CRP (SMD = −0.48; 95% CI, −0.96 to 0; $P = 0.049$). However, studies were heterogeneous, and when removing one study that treated subjects with both selenium and CoQ10 in doses >200 mg/day from the analysis, the relationship between selenium administration and CRP was no longer significant by visual inspection of forest plot (*P*-value not provided by authors). Furthermore, another study included in the analysis administered selenium together with zinc to participants, and not alone. Only two of the included studies administered selenium alone, neither of which found significant decreases in serum CRP.
Tomatoes and lycopene[132]	Systematic review and meta-analysis of seven RCTs[a], 4 of which were included in the tomato treatment analysis, and four into the lycopene treatment analysis with respect to serum CRP measurements. Treatment duration ranged from 20 days to 12 weeks.	Diverse. Studies included healthy participants and those with diverse comorbidities and BMI ranges. Mean participant ages ranged from ~23 to 65.	Total of 676 participants across the seven studies analyzed with one overlapping study (lycopene = 334, tomato = 404). Female% ranged from 0 to 100%, with a mean of 46%.	Neither tomato supplementation nor lycopene administration significantly improved serum CRP. The overall standard mean difference for tomato supplementation was −0.14 (95% CI −0.34 to 0.05), and for lycopene administration was −0.03 (95% CI −0.28 to 0.23).
Zinc[133]	Systematic review and meta-analysis of eight RCTs	Diverse. No study included completely healthy individuals, except one were all participants were elderly.	Total of 417 participants. Female% was not reported. However, three out of the eight studies focused exclusively on females.	Zinc administration overall decreased plasma CRP by a WMD of −1.68 mg/L (95% CI: −2.4 to −0.9, $P < 0.001$). However, as the authors point out, studies where doses of zinc were 50 mg/day (higher dose), those that were of poor quality, and studies observing participants with renal dysfunction,

Continued

Table 1 *Continued*

Supplement	Study type + duration	Participant characteristcs	# of participants	Results
				observed larger decreases in CRP in its treatment groups as compared with good quality studies of healthier participants.
Melatonin[134]	Systematic review and meta-analysis of four RCTs[a]—treatment duration ranged from 1 to 3 months.	Participants were non-healthy in the studies, with a wide range of ages in two studies (mean values not reported), and means of ~60 years in one study, and ~66 years in another.	Total of 240 participants. Female% is not reported.	Melatonin administration was overall found to significantly reduce serum hs-CRP levels (standard mean difference = −1.80; 95% CI −3.27 to −0.32, $P = 0.01$) between intervention and placebo groups. When comparing the intervention group to itself at baseline, the hs-CRP decrease was still significant, but smaller (SMD = −1.13; 95% CI −1.70 to −0.55, $P < 0.001$). However, the study did not account for weight loss as a possible confounder in its analysis of studies.
Vitamin D[135]	Systematic review and meta-analysis of 33 RCTs—Treatment duration ranged from 6 weeks to 12 months in studies of non-pregnant patients, and in pregnant patients from 6 weeks to 24–28 weeks of gestation until delivery.	Studies predominantly looked at patients with Type 2 diabetes mellitus (with or without other comorbidities), and pregnant patients with gestational diabetes mellitus. Among the former, mean participant ages hover around the mid-to-late 50s.	Total of 2067 participants across all groups, of which 475 were pregnant women.	Vitamin D supplementation significantly decreased serum hs-CRP in diabetic patients, with a weighted mean difference (WMD) = −0.27 (95% CI −0.35 to −0.20; $P < 0.001$). The authors found significant heterogeneity across studies based on disease state. They also found evidence of publication bias for vitamin D with respect to its impact of hs-CRP ($P < 0.001$). Study also did not account of weight changes in those receiving vitamin D as compared with placebo.
Vitamin D[136]	Systematic review and meta-analysis of 9 RCTs with duration >12 weeks and a Jadad score of 3 or greater.	Studies predominantly evaluated non-healthy individuals. Mean ages vary greatly between studies.	Total of 1984 participants. Female % is not reported.	Vitamin D supplementation did not significantly reduce serum CRP overall (WMD = −0.324 ml/L; 95% CI −1.01 to 0.36; $P = 0.067$). Studies where vitamin D supplementation was ≥ 1000 IU/day saw a statistically significant decrease in CRP (WMD = −0.939; 95% CI −1.805 to −0.073; $P = 0.034$), but with significant heterogeneity between studies.
Ginger[137]	Systematic review and meta-analysis of five RCTs[a] with durations of 10 weeks to 3 months, with one study not mentioning duration.	Studies predominantly evaluated non-healthy individuals. Mean ages vary greatly between studies.	Total of 155 participants. Female% is not reported.	Ginger supplementation significantly reduced serum CRP (WMD = −0.84 mg/L; 95% CI −1.38 to −0.31), and analysis did not reveal publication bias. It is interesting to note that the authors found the amount of decrease in serum CRP to be independent of the dosage of ginger administered to participants. Weight changes between study participants were not discussed in the study, and could serve as a significant potential confounder.
Multivitamins and minerals[138]	Systematic review and meta-analysis of 18 RCTs[a] of durations between 1 week and 3 years.	Studies varied, including an approximately even number of studies focusing on healthy and non-healthy participants. Mean ages vary greatly between studies.	Total of 1747 participants. Female % is not reported.	Supplementation with a large variety of vitamins and minerals found no impact on serum CRP (WMD = −0.491; 95% CI −0.789 to 0.193; $P = 0.001$).

[a]Original paper included more studies, but only this number of included studies also measured CRP.

CI: −3.52 to 3.26). Random-effects meta-regression revealed that changes in serum CRP levels were independent of the dosage of magnesium supplementation (slope: −0.004; 95% CI: −0.03 to 0.02; $P = 0.720$) or duration of follow-up (slope: −0.06; 95% CI: −0.37 to 0.24; $P = 0.681$).[139] Another meta-analysis of 11 RCTs revealed that magnesium treatment was not found to significantly affect plasma concentrations of CRP (WMD: −0.11 mg/L, 95% CI: −0.75 to 0.52, $P = 0.727$), however, when the analysis was stratified to compare subgroups of studies in populations with baseline plasma CRP values of ≤3 and >3 mg/L, a significant reduction of CRP values was observed in the subgroup with high baseline CRP (WMD: −1.12 mg/L, 95% CI: −2.05 to −0.18, $P = 0.019$).[140–143] Further well-designed studies are still necessary to confirm these results.

- *Melatonin* was also investigated with a meta-analysis of six trials, which found significant decreases in CRP and IL-6 in patients with metabolic syndrome (SMD = −1.80; 95% CI −3.27 to 0.32; $P = 0.01$) and SMD = −2.02; 95% CI −3.57 to −0.47; $P = 0.01$, respectively).[134] Confounding factors, such as changes weight between groups, were unfortunately also not accounted for.
- *Vitamin D* supplementation has been extensively studied. In patients with diabetes mellitus, the meta-analysis of 33 studies showed a slight decrease in hs-CRP (WMD −0.27 mg/L; 95% CI −0.35 to −0.20; $P < 0.001$).[135] Without specifically investigating diabetic patients, another study found a significant decrease of CRP in patients supplemented with vitamin D, however, the authors urge caution in interpreting the results due to study heterogeneity.[141] Two other meta-analyses, one evaluating nine high-quality prospective studies[136] and another looking at overweight and obese subjects specifically[142] did not find any impact of vitamin D supplementation on CRP.
- *Ginger* was evaluated in a meta-analysis by Mazidi *et al.* looking at nine studies of ginger supplementation vs. placebo. They found significant decreases in serum CRP (WMD = −0.84 mg/L, 95% CI −1.38 to −0.31).[137] However, most patients in the studies analyzed were either diabetic or using dialysis, and the paper did not account of weight changes between treatment and placebo arms.
- *Broad vitamin and mineral supplementation* was also assessed in a meta-analysis of 18 trials evaluating both healthy and non-healthy patients given multivitamin and mineral preparations, and did not find any significant differences in either CRP or IL-6 compared with placebo.[138]

In conclusion, besides those several nutraceuticals presented in the recent ILEP recommendations, no high-quality evidence currently exists for most of the above natural substances with respect to changes in blood CRP, and current evidence suffers from potential significant confounders. Magnesium, selenium, zinc, and melatonin supplementations are supported by very weak evidence, and more research accounting for significant confounding factors, such as changes in weight, BMI, and WC, are necessary before a conclusion can be drawn.

Take home message and recommendations

This narrative review discusses the role that systemic inflammation plays in CV morbidity and mortality, the molecules associated with this process, and the evidence behind therapies aimed at reducing subclinical inflammation. The relationships between hs-CRP, Lp(a), and oxLDL, and CVD are clearly established, though the relationship between circulating Lp(a) and atheroma volume is not as robust in all patient populations,[33] and more research is needed before the inflammation-triggering properties of oxLDL and Lp(a) can be fully quantified and understood. With respect to a direct mortality benefit in the reduction of subclinical inflammation, a strong relationship has been established in the case of inflammation measured using circulating levels of hs-CRP,[56,57,59,60] though the same cannot be said of Lp(a) and oxLDL levels due to multiple confounding factors seen in the studies currently available.

Author contributions

All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Lead author biography

Dr Richard Webb is currently a Lecturer in Clinical Nutrition at Liverpool Hope University, United Kingdom. He is passionate about understanding the links between lipid-mediated cardiovascular disease and nutrition by using a range of molecular and population-based approaches. He is also particularly interested in how to better prevent and manage the condition using dietary strategies.

Data availability

All data are included in the submission/manuscript file.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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