The Anti-Inflammatory Effects of Statins on Coronary Artery Disease: An Updated Review of the Literature

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Abstract: Background: Statins have long been used for the protection against coronary artery disease (CAD). Their beneficial effect apart from cholesterol reduction lies in their pleiotropic properties. Emerging evidence from laboratory studies and clinical trials as well have pointed out the pivotal role of inflammation on the initiation and exacerbation of atherosclerosis; a major cause of CAD. Inflammation markers such as high sensitivity C-reactive protein and adhesion molecules are shown to increase in CAD patients and are used as prognostic tools. It is well known that statins can actually reduce the circulating levels of these agents slowing therefore the inflammatory process; interestingly not all types have the same outcome.

Conclusion: The anti-inflammatory effect of statins on the formation of atherosclerotic plaque and the function of endothelial cells is thus of particular importance as these agents can actually ameliorate CAD prognosis.

Keywords: Statins, inflammation, pleiotropic effect, coronary artery disease, CRP, CAD prognosis.

1. INTRODUCTION

Heart disease is the leading cause of death in modern Western culture [1]. The main factor behind heart disease is the hardening and loss of normal functioning of the coronary arteries (atherosclerosis). Atherosclerosis occurs because of mineralization and oxidized cholesterol in the vessel walls. The whole process starts with and gets worsen under inflammatory conditions [2]. Atherosclerosis is a complex inflammatory process characterized by the presence of monocytes or macrophages and T-lymphocytes in the atheroma, the inflammatory cytokines are secreted which modify endothelial function, proliferation of VSMCs, degradation of collagen, and thrombosis [3]. An early phase of atherogenesis is the adhesion of monocytes to endothelium and their penetration into the subendothelial spaces. Decreased elasticity results in a reduction in vascular range, which causes decreased blood supply to the heart and other organs, such as the brain or kidneys. Reduced blood supply leads to impaired function of specific organs and tissues. This is the same mechanism that leads to aging and, through the aging process, ultimately affects every cell in the body. However, while in most cases the function of other organs deteriorates progressively, in the case of coronary artery disease, the first symptom is often sudden death. Therefore, it is the disease that oftentimes does not allow for second chances.

Statins have long been used as treatment for atherosclerosis and heart disease (Clinical trials on Statins are summarized in Table 1) [4-11]. Their beneficial effects lie in their anti-inflammatory properties, which are exhibited by a reduction in the release of C-reactive peptide, chemokines, cytokines, and adhesion molecules, as well as modulation of T-cell activity [12]. Furthermore, statins inhibit the transendothelial migration of leukocytes due to a decrease in the expression of adhesion molecules such as ICAM-1, lymphocyte function-associated antigen-1, and monocyte chemoattractant protein-1. Statins further prevent inflammation by inhibiting chemokine release and Th1-type chemokine receptors on T cells [13-17].

2. PLEIOTROPIC EFFECTS OF STATINS

Statins are competitive inhibitors of 3-hydroxy-3-methylglutartic coenzyme A (HMGCoA), a key enzyme in the biosynthesis of cholesterol that converts HMGCoA to mevalonate [18].

Currently, available statins can be classified into two categories: a) natural statins and b) synthetic statins [2]. Natural statins include lovastatin, which is a metabolite of a fungus and synthetic derivatives of pravastatin and simvastatin. Fluvastatin and atorvastatin are fully synthetic substances with completely different chemical structures. The third synthetic statin, cerivastatin, was withdrawn from the market in 2001 because of many referred severe cases of rhabdomyolysis [18].
The mechanism of action of statins is to capture a part of the HMGCoA-binding region in HMGCoA-reductase, preventing thus access of the substrate to the active site of the enzyme. All the above statins have an area that resembles the HMG, which may be present as an inactive lactone ring [19]. In vivo, these prodrugs are enzymatically hydrolysed to the active hydroxy-acid form. Based on the groups that bind to the position of HMG in the reductase, another classification of statins can be: Type I, which have hydrophobic groups and are similar in structure to compactin (mevastatin) and Type II, which are completely synthetic and have greater binding groups ranging from low to very hydrophobic [19].

Due to inhibition of the biosynthetic pathway of cholesterol caused by statins, they are considered as the drugs that

| Study | Design | Population | Type of statin | Clinical outcomes | Conclusions |
|-------|--------|------------|----------------|-------------------|-------------|
| 45[4] | Randomized, double blind, placebo-controlled trial | 4,444 individuals aged 35–70 years with a history of CHD | Simvastatin 20–40 mg vs. placebo | Primary end point: total mortality Second end point: time to first major coronary event | Simvastatin reduced deaths [RR = 0.70 (95% CI 0.58–0.85, P = 0.0003)] and major coronary events[RR = 0.66 (95% CI 0.59–0.75, P <0.00001)] |
| JUPITER [5] | Randomized double-blind, placebo-controlled trial | 17,802 healthy individuals with normal LDL cholesterol and elevated hsCRP level (≥2 mg/l) | Rosuvastatin 20 mg vs placebo | Primary end point: occurrence of first major cardiovascular event | Rosuvastatin reduced the risk of major cardiovascular events (HR = 0.56, 95% CI 0.46–0.69, P <0.0001) |
| PROVE IT-TIMI 22 [6] | Randomized, double-blind trial | 4,162 patients with ACS | 80 mg Atorvastatin vs. 40 mg Pravastatin | Primary end point: composite of death from any cause, myocardial infarction, unstable angina requiring rehospitalization, revascularization and stroke | Atorvastatin reduced risk for death or CV events by 16% (95%CI, 5-26%) |
| WOSCOPS [7] | Randomized, double-blind, placebo-controlled trial | 6,595 men aged 45–64 years with no history of myocardial infarction(mean cholesterol level=7 mmol/l) | Pravastatin 40 mg vs placebo | Primary end point: composite of nonfatal myocardial infarction and death from coronary heart disease | Pravastatin reduced coronary events compared to placebo [RR reduction, 31% (95% CI 17–43%, P<0.001)] |
| TNT[8] | Randomized, double-blind trial | 10,001 patients (81% male, mean age 61 years) with clinically evident CHD(LDL cholesterol <3.4 mmol/l) | Atorvastatin 10 mg vs 80 mg | Primary end point: composite of major coronary events | Reduced primary events in atorvastatin 80 mg group compared to the 10 mg per day group (HR 0.78, 95% CI 0.69–0.89, P <0.001) No difference in overall mortality |
| IDEAL[9] | Prospective, randomized, open-label, blinded end point evaluation trial | 8,888 patients (mean age 62 years, 81% male) aged <80 years with a history of AMI | Simvastatin 20 mg vs atorvastatin 80 mg | Primary end point: coronary death, confirmed nonfatal AMI or cardiac arrest with resuscitation Composite secondary end point: major cardiovascular events (primary end points plus stroke) | Reduced events in the atorvastatin group (HR = 0.89, 95% CI 0.78–1.01, P = 0.07) No difference in the risk of death from any cause Composite secondary end point was reduced in the atorvastatin group (HR = 0.87, 95% CI 0.78–0.98, P = 0.02) |
| PROSPER [10] | Randomized, double-blind, placebo-controlled trial | 5,804 elderly (mean age 75 years) with pre-existing vascular disease or risk factors | Pravastatin 40 mg per day vs placebo | Primary end point: composite of major coronary event | Pravastatin reduced major cardiovascular events (HR = 0.85, 95% CI 0.74–0.97, P = 0.014) |
| SHARP [11] | randomised double-blind trial | 9,270 patients with chronic kidney disease (3023 on dialysis and 6247 not) with no known history of myocardial infarction or coronary revascularisation. | simvastatin 20 mg plus ezetimibe 10 mg daily vs. placebo | Primary end point: first major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure) | Reduced risk of major vascular events (RR=0.83, 95% CI 0.74–0.94) in simvastatin + ezetimibe group |
have most significantly changed the treatment of hypercholesterolemia since their introduction into clinical practice about 20 years ago. They are thought to be the most effective medications for reducing plasma cholesterol and are relatively well tolerated when ministered. Furthermore, angiographic studies have shown that they reduce the development of atherosclerosis and may cause its regression [20]. These actions have translated into a significant reduction in cardiovascular mortality and morbidity, as shown in many clinical studies (WOSCOPS, AFCAPS / TexCAPS, HS, CARE, LIPID, HPS) [2]. In most of these studies, the reduction of LDL cholesterol is highlighted as the main factor for the reduction of cardiovascular risk. The widespread use of statins internationally has also highlighted their frequent side effect, myopathies, which in most cases are mild but they can even lead to rhabdomyolysis.

In recent years, primarily in laboratory findings on the action and biological effects of statins, there has been intense discussion about the possibility that many of the beneficial effects of statins, beyond the reduction of cholesterol, are due to other types of actions described as pleiotropic [21].

The first comments on the pleiotropic effects of statins were made after researchers had observed that the overall benefits of the use of statins were larger than what one would expect based solely on the reduction in lipid levels. Some of the pleiotropic effects of statins are improving the function of vascular endothelial cells, enhancing the stability of atherosclerotic plaque, reducing oxidative stress and inflammation, and causing extrapathic effects on the immune system, central nervous system, and bones [21].

Many of the pleiotropic effects are mediated by the inhibition of isoprenoids which can act as intracellular signalling molecules [22]. Such molecules are farnesyl pyrophosphate (FPP) and geranyl geranyl pyrophosphate (GGPP).

Therefore, the isoprenoids are involved in post-translational modification of proteins, such as nuclear laminins, Ras, Rho, Rac, and Rap. Since isoprenylated proteins may control various intracellular functions, it is not surprising that statins have other effects besides lipid reduction.

Specifically, the pleiotropic effects of statins have been associated with a cardioprotective effect, the slowing of the progression of renal damage, the glucose metabolism, and bone regeneration.

A summary of the pleiotropic effects of statins and the associated molecular pathways are illustrated in the table below [22] (Table 2).

### 3. ANTI-INFLAMMATORY EFFECTS OF STATINS

The cells interact with each other and with the extracellular matrix, promoting the normal functional and structural integrity of tissues [23]. Many types of cells and molecules are involved in inflammation. Histamine, C3a, C5a, bradykinin, leukotriene C, leukotriene D and leukotriene E increase vascular permeability; C5a, leukotriene B4, chemokines are related with chemotaxis; nitric oxide and prostacyclin with vasodilatation; TNF, IL-1 and IL-6 with systemic signs and leukocyte lysosomal enzymes, nitric oxide and reactive O2 with tissue destruction. Some of these trigger, multiply, or maintain the complex process of inflammation while others inhibit, at different times in the development of inflammation [22].

The inflammatory response in the connective tissue of blood vessels involves blood vessels (endothelium), plasma components, circulating blood cells (e.g. neutrophils, monocytes, lymphocytes, platelets), and cellular and extracellular components of connective tissue [23]. Depending on the injury, inflammatory cells permeate the vascular endothelium and are involved in the generation of renal damage, the glucose metabolism, and bone regeneration.

### Table 2. Pleiotropic effects of statins [15].

| Inflammation/Immunomodulation                                                                 | Atherosclerotic Plaque Stability                              |
|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| ↓ Suppression of the transcription factor NFXB                                                | ↓ Inflammatory cell infiltrate                                |
| ↓ Chemokines (MCP1, RANTES) and cytokines (IL-1B, TNF, IL-6, IL-8)                            | ↓ MMP synthesis                                               |
| ↓ Adhesion molecules (P-selectin, VLA4, ICAM-1)                                               | ↓ Macrophage accumulation                                    |
| ↓ MHC Class II (via -IFN-γ)                                                                  | ↑ collagen synthesis                                          |
| ↓ Activity of T cells (blockage of LFA1)                                                     | ↑ vascular smooth muscle cell content                         |
| ↓ Monocyte activation                                                                       |                                                               |
| ↓ CRP levels                                                                                |                                                               |
| ↑ NO levels                                                                                 |                                                               |
| ↑ anti-inflammatory prostacyclins activation of the PLAX2-COXpathway                        |                                                               |

| Oxidative stress | Endothelial function and angiogenesis | Antithrombotic and antiplatelet |
|------------------|--------------------------------------|----------------------------------|
| ↓ NADPH Oxidase and superoxide formation          | ↑ Enos production, activity       | ↓ Platelet aggregation (-tissue factor expression) |
| ↓ LDL oxidation                                      | ↓ endothelin-1                     | ↓ Platelet activation (-CD40L, PECAM-1, IL-1, P-Selectin, isoprenoids, +Enos) |
| ↑ Oxygen free radical scavenging                    | ↑ Endothelial progenitor cells (EPC)| ↑ Tissue-type plasminogen activator |
|                                                               | ↑ PI-3 kinase/ Akt activity        |                                   |

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| ↑ NO levels                                                                                 |                                                               |
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| ↑ Oxygen free radical scavenging                    | ↑ Endothelial progenitor cells (EPC)| ↑ Tissue-type plasminogen activator |
|                                                               | ↑ PI-3 kinase/ Akt activity        |                                   |
dues monocyte adhesion to vascular endothelium by reduc-
mechanism of anti-inflammatory properties. There are findings supporting the anti-inflammatory effects of statins, including the reduction of the levels of C-reactive protein (CRP) in subjects taking a statin regardless of the levels of decrease in LDL cholesterol [5, 24-37]. Furthermore, in vitro models have shown that statins inhibit molecules such as NF-κB, TNF-α, IL-1b, which are involved in the inflammatory response [36]. These anti-inflammatory effects are of particular importance in preventing the formation of atherosclerotic plaque and to the functioning of endothelial cells.

It has been suggested that treatment with atorvastatin significantly improves markers of endothelial function and inflammation in patients with diabetes, but some studies do not seem to support that outcome [35, 38]. The way that atorvastatin treatment affects patients with diabetes mellitus is that it acts directly on key intracellular transcriptional pathways by reducing the expression of TNF-α and other pro-inflammatory cytokines [39].

Nevertheless, evidence from clinical and laboratory trials underline a 10-12% increase in new-onset diabetes mellitus (NODM) among patients receiving statins probably due to increased insulin resistance, impaired β-cell function or both [40, 41]. The risk of developing NODM during statin therapy seems to be dose-dependent and increases in individuals with pre-existing risk factors like age >70 years, women, Asian ethnicity, metabolic syndrome [9, 42-45]. Pitavastatin is thought to be the only statin that does not affect glucose metabolism or NODM development when compared with placebo or other statins [46-49]. However, the benefit in preventing cardiovascular events clearly exceeds any potential risk of diabetes and therefore doctors should not hesitate to prescribe them when necessary and monitor blood glucose and HbA1c levels in high risk patients [50].

Furthermore, statins have been shown to decrease the number of inflammatory cells in atherosclerotic lesions and to possess other anti-inflammatory properties [51]. They have been proven to act as anti-inflammatory agents that slow the progression of disease [3]. The exact mechanism has not been clarified, but may lie in the inhibition of adhesion molecules such as intercellular adhesion molecule 1 or cytokines such as interleukins 6 and 8, which are involved in the accumulation of inflammatory cells [52]. It is remarkable that a study has shown that statins can mitigate the inflammatory response, independent of the inhibition of HMG-CoA reductase, by binding directly to a novel regulatory site of β2 integrin, the antigen 1 of leukocyte functionality [52]. The mechanism of anti-inflammatory properties of statins is further clarified by a study which showed that cerivastatin reduces monocyte adhesion to vascular endothelium by reduc-

A clinical indicator of inflammation is the high-sensitivity C-reactive protein (hs-CRP), which is an acute phase protein produced by the liver in response to proinflammatory cytokines, such as interleukin 6, and which reflects a low level of systemic inflammation. Elevated levels of hs-CRP have been shown to be predictive of an increased risk of coronary heart disease in apparently healthy adults, as the hs-CRP is increased in patients with coronary heart disease, ischemia, and heart attack [54]. Indeed, it has been suggested that CRP contributes to the development of atherosclerosis, since its binding to modified LDL molecules within atherosclerotic plaques activates the complement which then promotes the development of lesions [5]. In JUPITER, a randomized, double-blind, placebo controlled, multicenter trial, researchers evaluated the effect of a 20mg daily dose of rosuvastatin in the rates of first major cardiovascular events in apparently healthy individuals with normal low-density lipoprotein (LDL) cholesterol levels (<130 mg per deciliter) and elevated high-sensitivity CRP levels. Apart from 37% reduction in the high-sensitivity CRP levels, a significant reduction was recorded in the incidence of major cardiovascular events [5]. Furthermore, other studies have revealed that CRP adversely affects the endothelial function by reducing the expression of eNOS in cultivated endothelial cells [36].

CRP has also been suggested to predict future cardiovascular events [51]. Therefore, new approaches to the treatment of cardiovascular disease have focused on the reduction of CRP levels [55, 56].

4. PRECLINICAL EVIDENCE OF STATINS’ ANTI-INFLAMMATORY EFFECT

A recent study provided in vivo evidence that pitavastatin reduces inflammation within atherosclerotic lesions in mice with chronic renal disease [26]. In this study, researchers found that pitavastatin had decreased pro-inflammatory osteopontin in the plasma of chronic renal disease mice (P<0.05). An earlier study on mice had established the anti-inflammatory effects of simvastatin beyond its plasma cholesterol–lowering activity [29]. According to the researchers’ observations, simvastatin has a strong anti-inflammatory activity even in small doses (3mg/kg). Another study showed that simvastatin can inhibit vascular inflammation in ApoE– mice [57]. This was in contrast with an earlier study on mice with endotoxic-induced lung injury, which showed that simvastatin exhibited no anti-inflammatory activity, whilst atorvastatin and pravastatin had an effect on inflammation [58]. Furthermore, a recent study based on the hypothesis that statins can improve aneurysm healing after endovascular treatment due to their anti-inflammatory effects, showed no such outcome [37]. However, Manitsopoulos et al. demonstrated that high-dose simvastatin prevents experimental hyperinflation lung injury through its angioprotective and anti-inflammatory effects [59]. Preclinical studies regarding statins’ anti-inflammatory effects are summarized in Table 3 [22, 28, 30, 59-62].
5. CLINICAL EVIDENCE OF STATINS' ANTI-INFLAMMATORY EFFECT

We have mentioned above that statins can affect the process of inflammation through various pathways. Several studies have investigated the significant effect of the use of the different statins.

Brili et al. investigated the effects of atorvastatin on endothelial function and low-grade systemic inflammation in subjects with successful surgery for aortic coarctation repair (SCR). According to their results, the treatment with atorvastatin was proven significantly beneficial for the subjects, since it was shown to improve endothelial function and decrease circulating levels of proatherogenic inflammatory cytokines, IL-1β, adhesion molecules, and sVCAM-1, mediating thus the suppressed systemic inflammatory status [25].

Earlier, researchers conducting the PRINCE study aimed to test the hypothesis according to which the reduction in CRP due to pravastatin could confirm its anti-inflammatory effect [24]. There were two trials carried out, a randomized, double-blind trial and an open-label study, which both concluded that the decrease in CRP levels observed among patients who received pravastatin was independent of the LDL-C levels. Therefore, pravastatin showed an anti-inflammatory effect in addition to its lipid-lowering effects, which strongly supports the hypothesis. Further support was given by the results of a study testing the anti-inflammatory effects of another statin, rosuvastatin [26]. The study compared anti-inflammatory effects and lipid profiles in patients with coronary artery disease (CAD) and similar LDL-C levels and found that both groups tested experienced anti-inflammatory effects but that the inflammatory markers did not significantly differ in patients with CAD taking rosuvastatin [26]. Similarly, Shabzazian et al. found simvastatin to lower the serum levels of CRP and IL-6, main indicators of inflammation, in hemodialysis patients [29].

The statin most investigated regarding its anti-inflammatory effects is atorvastatin. A study by Navarro et al. showed that the CRP levels in patients under dialysis and those with diabetes or hyperlipidemia were reduced from 5.4mg/l to 2.3mg/l, whereas in the study of Vernaglione et al., the reduction was from 9mg/l to 5mg/l and Panichi et al. observed a decrease from 2.6mg/l to 2mg/l in patients with chronic heart failure [30, 31, 36]. A significant effect of atorvastatin on CRP levels was shown in the study of Macin et al., where the quantitative and proportional reduction in the atorvastatin group was much higher than in the placebo group (-62% versus -11% at discharge, -84% versus -30% at 1 month), which was in accordance with the findings of the

Table 3. Preclinical studies on statins’ anti-inflammatory effects.

| Study            | Population | Type of statin | Intervention                                                                 | Results                                                                 |
|------------------|------------|----------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Shibasaki et al. [15]. | CRD mice   | Pitavastatin, Simvastatin, | Control mice, CRD mice, and CRD mice treated with 100 mg/kg diet (0.01% wt/wt) for 10 weeks | Reduced inflammation within atherosclerotic lesions (-59.4 ± 9.8%; P<0.01) |
| Sparrow et al. [17]. | Mice deficient in apoE | Simvastatin      | 100 mg/kg body wt of simvastatin daily for 6 weeks                          | Anti-inflammatory activity (P<0.02)                                      |
| Brinjikji et al. [27]. | A rabbit model of unruptured intracranial aneurysms | Simvastatin | two groups: control group, rabbits receiving simvastatin orally             | No significant differences in the mean aerysm size and in the histologic grade of occlusion (statin group 2.6±0.8 vs control group 2.7±3.2, p=0.94). No coil compaction. |
| Liu et al. [40] | Five-week old ApoE-/- mice and wild-type C57BL/6 mice | Simvastatin | ApoE-/- mice: simvastatin (50 mg·kg-1·d-1) or vehicle by gavage, wild-type mice: vehicle | Simvastatin inhibits vascular inflammation and atherosclerosis in ApoE-/- mice, probably through downregulation of the HMGB1-RAGE axis. |
| Melo et al. [41] | male C57BL/6 mice, 8 to 10 weeks old | atorvastatin, pravastatin, simvastatin | LPS (10 mg/kg), LPS plus atorvastatin (10 mg/kg/day; A + LPS group), LPS plus pravastatin (5 mg/kg/day; P + LPS group), LPS plus simvastatin (20 mg/kg/day; S + LPS group), control group received saline. | Atorvastatin and pravastatin but not simvastatin exhibit anti-inflammatory and antioxidant activity in endotoxin-induced acute lung injury |
| Manitsopoul os et al. [42] | Male C57BL/6 mice | Simvastatin | Four groups (n=7/group): control groups and injury groups were pre-treated with simvastatin and mechanical ventilation with different tidal volume and respiratory rate | High-dose simvastatin prevents hyperinflation lung injury by angioprotective and anti-inflammatory effects |
The study of Xia et al. investigated whether patients with stable coronary artery disease who are receiving chronic statin treatment and undergoing noncardiac emergency surgery benefit from acute atorvastatin reload. Their results suggest that atorvastatin reload reduces 30-day incidence of major adverse cardiac events by 65% (odds ratio 0.35, 95% confidence interval 0.18–0.86; p=0.005) [64].

Statins have been reported to have positive effects on the outcome of unstable angina, STEMI and NSTEMI incidences. A study by O’Brien et al. investigated the association of both NSTEMI and unstable angina with statin therapy. They found that the reduction of LDL-C due to statins resulted in later presentation of NSTEMI and unstable angina [65].

Mytas et al. found that early treatment with statins in patients who present with STEMI results in a decrease of systemic inflammation, a lesser degree of myocardial damage, and a possible reduction in short-term mortality [66]. Similar results were found in the study of Aydin et al. where both rosuvastatin and atorvastatin lowered the inflammation markers in STEMI patients, whereas in another study, a loading dose of atorvastatin was found to reduce inflammatory response and myocardial dysfunction in STEMI patients [67, 68]. The inflammatory response has also been found to be reduced in percutaneous coronary intervention when a short-term high-dose atorvastatin treatment is administered [69]. How atorvastatin reduces inflammatory response in percutaneous coronary intervention was investigated by Yang et al, who found that it is possibly due to attenuation of inflammatory response in monocytes via PPARγ activation [70]. Furthermore, the protective effect of statins in patients with unstable angina was found to be due to the expression of multiple microRNAs in the blood stream [71].

CONCLUSION
As inflammation, oxidative stress, coagulation disorders, and endothelial dysfunction all play a role in atherosclerosis, it is reasonable to assume that the improvement of these parameters will have a beneficial effect in the prevention of cardiovascular disease. However, we have not been able to document how significant the role of pleiotropic action of statins is in preventing cardiovascular disease, because it is very difficult for the appropriate studies to be designed.

As we have seen in our review, statins have been proven to have a positive effect on the reduction of inflammation in patients with various diseases such as coronary artery disease, chronic renal disease, and diabetes mellitus. All statins examined were shown to lower the levels of inflammatory markers and especially CRP levels. However, the effect on inflammation differs between various types of statins, with some demonstrating more significant results compared to others. Nonetheless, statins were arguably proven to be an effective treatment as far as the inhibition of inflammation is concerned.

CONSENT FOR PUBLICATION
Not applicable.

CONFLICT OF INTEREST
The authors confirm that this article content has no conflict of interest.

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