Send Orders for Reprints to reprints@benthamscience.ae

Current Cardiology Reviews, **2017**, *13,* **209-216**

REVIEW ARTICLE

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

Evangelos Diamantis*, George Kyriakos, Lourdes Victoria Quiles-Sanchez, Paraskevi Farmaki, Theodoros Troupis

Department of Anatomy, School of Medicine, University of Athens, Athens, Greece

ARTICLE HISTORY

Received: January 23, 2017
Revised: April 12, 2017
Accepted: April 17, 2017

DOI:
10.2174/1573403X13666170426104611

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.

*Address correspondence to this author at the Department of Anatomy, School of Medicine, University of Athens, 75 Mikras Asias Street, Athens 11527, Greece; Tel: 00302107462508; Fax: 00302107462398; E-mail: vaggelisd01@gmail.com

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 chemotactic 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-methylglutaric 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].

1573-403X/17 $58.00+.00

Table 1. Clinical trials of statins major coronary event (coronary death, definite or probable nonfatal myocardial infarction, resuscitated cardiac arrest and definite silent myocardial infarction), CVD: cardiovascular disease, AMI: acute myocardial infarction, CHD: chronic heart disease, LDL: low density lipoprotein, hsCRP: high-sensitivity C-reactive protein.

Study	Design	Population	Type of statin	Clinical outcomes	Conclusions
4S [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 Secondary 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 elevatedhsCRPlevel (≥2 mg/l)	Rosuvastatin 20 mgvs placebo	Primary end point: occurrence of first major cardiovascular event	Rosuvastatinreduced the risk of major cardiovascular events (HR = 0.56, 95% CI 0.46–0.69, *P* <0.00001)
PROVE IT-TIMI 22 [6]	Randomized, double-blind trial	4.162 patients with ACS	80mg 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 mgvs atorvastatin 80mg	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	9270 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

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

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 extrahepatic 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 0_2 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 endothe-

Table 2. Pleiotropic effects of statins [15].

Inflammation/Immunomodulation	Atherosclerotic Plaque Stability
↓ Suppression of the transcription factor NFκB	↓ 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 an activity	↓ Platelet aggregation (-tissue factor expression)
↓ LDL oxidation	↓ endothelin-1	↓ Platelet activation (-CD40L, PECAM-1, IL- 1, P-Selectin, isopreniods, +Enos)
↑ Oxygen free radical scavenging	↑ Endothelial progenitor cells (EPC)	↑ Tissue-type plasminogen activator
	↑ PI-3 kinase/ Akt activity	

lium and infiltrate tissues. The adhesion of inflammatory cells to vascular endothelium and dialysis in the inflammatory foci occurs through adhesion molecules. Then, inflammatory cells release proteolytic enzymes, nitric oxide, and free oxygen radicals, which foster catabolism and degradation of dead tissues, which are simultaneously phagocytosed and degraded by phagocytes (neutrophils and macrophages) [23].

Many of the beneficial effects of statins in tissues and organs are attributed to their 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-kB, o TNF-a, 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 plaques 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 reducing the expression of integrins and reduces actin polymerization by deactivating RhoA [53].

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].

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

Study	Population	Type of statin	Intervention	Results
Shibasaki *et al.* [15].	CRD mice	Pitavastatin,	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 aneurysm 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

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-1b, adhesion molecules, and sVCAM-1, meliorating 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

MIRACL study (-83% versus -74%) [28, 29]. On the other hand, Goicoechea et al. found atorvastatin to reduce not only the CRP levels but also TNF-α and IL-1β levels in patients with chronic kidney disease without modifying fibrinolytic balance [32]. Finally, Krane *et al*. found that CRP levels remained stable in patients with type 2 diabetes mellitus on hemodialysis when treated with atorvastatin [33].

However, it seems that not all statins have the same effects on inflammation. Nakagomi *et al.* examined whether different statins exert differing effects on inflammation, insulin resistance, and the progression of carotid atherosclerosis in patients with dyslipidemia [36]. As far as the inflammatory markers are concerned, pitavastatin caused a greater reduction in levels of TNF-α and MCP-1 (TNF-α: -36.0% versus -21.1%, MCP-1: -27.9% versus -10.9%) as well as hs-CRP (-32.1% versus -23.6%) compared to atorvastatin. Thus, the authors suggested that treatment with pitavastatin may be more beneficial than atorvastatin for reducing inflammation in patients with dyslipidemia [31]. Similarly, Khurana *et al.* compared the anti-inflammatory effects of atorvastatin and rosuvastatin in patients with acute coronary syndrome. They found out that, even though both statins lowered the CRP level, the use of rosuvastatin was more effective [35].

Some recent studies have investigated the effect of statin therapy on patients with stable coronary artery disease, and their results have shown a positive correlation between the therapy and the disease outcome. A study by Ndrepepa *et al.* examined the presentation patterns of patients with CAD when they are pretreated with statins. They found out that the presentation of unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) were higher in patients not taking statins but that stable angina was surprisingly higher in patients receiving the statins [63].

Leoncini *et al.* investigated the impact of high-dose atorvastatin on the pharmacodynamic effects of double-dose clopidogrel in statin-naive patients with stable coronary artery disease. This prospective, randomized study and concluded that there was a significant improvement on the pharmacodynamic effect of double-dose clopidogrel when combined with high-dose atorvastatin [64].

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.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. Nat Rev Drug Discov 2005; 4(12): 977-87.

[2] Tousoulis D, Papageorgiou N, Briasoulis A, Antoniades C, Stefanadis C. The failure of immunomodulation therapy in heart failure: does the statins "paradigm" prove the rule? Current Vasc Pharmacol 2010; 8(1): 114-21.

[3] Husain K, Hernandez W, Ansari RA, Ferder L. Inflammation, oxidative stress and renin angiotensin system in atherosclerosis. World J Biol Chem 2015; 6(3): 209-17.

[4] Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344(8934): 1383-9.

[5] Ridker PM, Danielson E, Fonseca FA, *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359(21): 2195-207.

[6] Cannon CP, Braunwald E, McCabe CH, *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350(15): 1495-504.

[7] Freeman DJ, Norrie J, Sattar N, *et al*. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001; 103(3): 357-62.

[8] LaRosa JC, Grundy SM, Waters DD, *et al*. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352(14): 1425-35.

[9] Waters DD, Ho JE, DeMicco DA, *et al*. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. J Am Coll Cardiol 2011; 57(14): 1535-45.

[10] Shepherd J, Blauw GJ, Murphy MB, *et al*. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360(9346): 1623-30.

[11] Baigent C, Landray MJ, Reith C, *et al*. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377(9784): 2181-92.

[12] Corsonello A, Garasto S, Abbatecola AM, *et al*. Targeting inflammation to slow or delay functional decline: where are we? Biogerontology 2010; 11(5): 603-14.

[13] Proksch E, Elias PM, Feingold KR. Regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity in murine epidermis. Modulation of enzyme content and activation state by barrier requirements. J Clin Invest 1990; 85(3): 874-82.

[14] Kapiotis S, Holzer G, Schaller G, *et al*. A proinflammatory state is detectable in obese children and is accompanied by functional and morphological vascular changes. Arterioscler Thromb Vasc Biol 2006; 26(11): 2541-6.

[15] Barrientos S, Brem H, Stojadinovic O, Tomic-Canic M. Clinical application of growth factors and cytokines in wound healing. Wound Repair Regen 2014; 22(5): 569-78.

[16] Jougasaki M, Ichiki T, Takenoshita Y, Setoguchi M. Statins suppress interleukin-6-induced monocyte chemo-attractant protein-1 by inhibiting Janus kinase/signal transducers and activators of transcription pathways in human vascular endothelial cells. Br J Pharmacol 2010; 159(6): 1294-303.

[17] Singh P, Kohr D, Kaps M, Blaes F. Influence of statins on MHC class I expression. Ann N Y Acad Sci 2009; 1173: 746-51.

[18] Kones R. Rosuvastatin, inflammation, C-reactive protein, JUPITER, and primary prevention of cardiovascular disease--a perspective. Drug Des Devel Ther 2010; 4: 383-413.

[19] Artom N, Montecucco F, Dallegri F, Pende A. Carotid atherosclerotic plaque stenosis: the stabilizing role of statins. Eur J Clin Invest 2014; 44(11): 1122-34.

[20] Banach M, Serban C, Sahebkar A, *et al*. Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies. BMC Med 2015; 13: 229.

[21] Koskinas KC, Windecker S, Raber L. Regression of coronary atherosclerosis: Current evidence and future perspectives. Trends Cardiovasc Med 2016; 26(2): 150-61.

[22] Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. Trends Mol Med 2008; 14(1): 37-44.

[23] van der Harst P, Voors AA, van Gilst WH, Bohm M, van Veldhuisen DJ. Statins in the treatment of chronic heart failure: biological and clinical considerations. Cardiovasc Res 2006; 71(3): 443-54.

[24] Libby P. Inflammation in atherosclerosis. Nature 2002; 420(6917): 868-74.

[25] Brili S, Tousoulis D, Antonopoulos AS, *et al*. Effects of atorvastatin on endothelial function and the expression of proinflammatory cytokines and adhesion molecules in young subjects with successfully repaired coarctation of aorta. Heart 2012; 98(4): 325-9.

[26] Albert MA, Danielson E, Rifai N, Ridker PM, Investigators P. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001; 286(1): 64-70.

[27] Yamazaki D, Ishida M, Watanabe H, *et al*. Comparison of anti-inflammatory effects and high-density lipoprotein cholesterol levels between therapy with quadruple-dose rosuvastatin and rosuvastatin combined with ezetimibe. Lipids Health Dis 2013; 12: 9.

[28] Shibasaki M, Wang JG, Figueiredo JL, *et al*. Pitavastatin reduces inflammation in atherosclerotic plaques in apolipoprotein E-deficient mice with late stage renal disease. PLoS One 2015; 10(9): e0138047.

[29] Shahbazian H, Atrian A, Yazdanpanah L, Lashkarara GR, Zafar Mohtashami A. Anti-inflammatory effect of simvastatin in hemodialysis patients. Jundishapur J Nat Pharm Prod 2015; 10(1): e17962.

[30] Sparrow CP, Burton CA, Hernandez M, *et al*. Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering. Arterioscler Thromb Vasc Biol 2001; 21(1): 115-21.

[31] Vernaglione L, Cristofano C, Muscogiuri P, Chimienti S. Does atorvastatin influence serum C-reactive protein levels in patients on long-term hemodialysis? Am J Kidney Dis 2004; 43(3): 471-8.

[32] Macin SM, Perna ER, Farias EF, *et al*. Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome: results of a randomized, double-blind, placebo-controlled study. Am Heart J 2005; 149(3): 451-7.

[33] Kinlay S, Schwartz GG, Olsson AG, *et al*. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. Circulation 2003; 108(13): 1560-6.

[34] Goicoechea M, de Vinuesa SG, Lahera V, *et al*. Effects of atorvastatin on inflammatory and fibrinolytic parameters in patients with chronic kidney disease. J Am Soc Nephrol 2006; 17(12 Suppl 3): S231-5.

[35] Krane V, Winkler K, Drechsler C, *et al*. Effect of atorvastatin on inflammation and outcome in patients with type 2 diabetes mellitus on hemodialysis. Kidney Int 2008; 74(11): 1461-7.

[36] Nakagomi A, Shibui T, Kohashi K, *et al*. Differential effects of atorvastatin and pitavastatin on inflammation, insulin resistance, and the carotid intima-media thickness in patients with dyslipidemia. J Atheroscler Thromb 2015; 22(11): 1158-71.

[37] Khurana S, Gupta S, Bhalla H, Nandwani S, Gupta V. Comparison of anti-inflammatory effect of atorvastatin with rosuvastatin in patients of acute coronary syndrome. J Pharmacol Pharmacother 2015; 6(3): 130-5.

[38] Sena CM, Matafome P, Louro T, Nunes E, Seica RM. Effects of atorvastatin and insulin in vascular dysfunction associated with type 2 diabetes. Physiol Res 2014; 63(2): 189-97.

[39] Tousoulis D, Papageorgiou N, Androulakis E, *et al*. Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches. J Am Coll Cardiol 2013; 62(8): 667-76.

[40] Banach M, Malodobra-Mazur M, Gluba A, Katsiki N, Rysz J, Dobrzyn A. Statin therapy and new-onset diabetes: molecular mechanisms and clinical relevance. Curr Pharm Des 2013; 19(27): 4904-12.

[41] Sattar N, Taskinen MR. Statins are diabetogenic--myth or reality? Atheroscler Suppl 2012; 13(1): 1-10.

[42] Culver AL, Ockene IS, Balasubramanian R, *et al*. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med 2012; 172(2): 144-52.

[43] Sattar NA, Ginsberg H, Ray K, *et al*. The use of statins in people at risk of developing diabetes mellitus: evidence and guidance for clinical practice. Atheroscler Suppl 2014; 15(1): 1-15.

[44] Sonal Sekhar M, Unnikrishnan MK. South-Asian population has a higher likelihood for diabetes risk for statins regardless of potency. Med Hypotheses 2015; 84(3): 283-4.

[45] Waters DD, Ho JE, Boekholdt SM, *et al*. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. J Am Coll Cardiol 2013; 61(2): 148-52.

[46] Yamakawa T, Takano T, Tanaka S, Kadonosono K, Terauchi Y. Influence of pitavastatin on glucose tolerance in patients with type 2 diabetes mellitus. J Atheroscler Thromb 2008; 15(5): 269-75.

[47] Teramoto T, Shimano H, Yokote K, Urashima M. New evidence on pitavastatin: efficacy and safety in clinical studies. Expert Opin Pharmacother 2010; 11(5): 817-28.

[48] Cho Y, Choe E, Lee YH, *et al*. Risk of diabetes in patients treated with HMG-CoA reductase inhibitors. Metabolism 2015; 64(4): 482-8.

[49] Vallejo-Vaz AJ, Kondapally Seshasai SR, Kurogi K, *et al*. Effect of pitavastatin on glucose, HbA1c and incident diabetes: A meta-analysis of randomized controlled clinical trials in individuals without diabetes. Atherosclerosis 2015; 241(2): 409-18.

[50] Sattar N, Preiss D, Murray HM, *et al*. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375(9716): 735-42.

[51] Tousoulis D, Andreou I, Tsiatas M, *et al*. Effects of rosuvastatin and allopurinol on circulating endothelial progenitor cells in patients with congestive heart failure: the impact of inflammatory process and oxidative stress. Atherosclerosis 2011; 214(1): 151-7.

[52] Weitz-Schmidt G, Welzenbach K, Brinkmann V, *et al*. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med 2001; 7(6): 687-92.

[53] Zhao X, Liu Y, Zhong Y, *et al*. Atorvastatin improves inflammatory response in atherosclerosis by upregulating the expression of GARP. Mediators Inflamm 2015; 2015: 841472.

[54] Tousoulis D, Koniari K, Antoniades C, *et al*. Combined effects of atorvastatin and metformin on glucose-induced variations of inflammatory process in patients with diabetes mellitus. Int J Cardiol 2011; 149(1): 46-9.

[55] Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002; 347(20): 1557-65.

[56] Yoshida M, Sawada T, Ishii H, *et al*. Hmg-CoA reductase inhibitor modulates monocyte-endothelial cell interaction under physiological flow conditions *in vitro*: involvement of Rho GTPase-dependent mechanism. Arterioscler Thromb Vasc Biol 2001; 21(7): 1165-71.

[57] Tousoulis D, Charakida M, Stefanadis C. Endothelial function and inflammation in coronary artery disease. Postgrad Med J 2008; 84(993): 368-71.

[58] Sposito AR, Aguiar Filho GB, Aarao AR, Sousa FT, Bertolami MC. Statins in acute coronary syndromes. Arquivos Brasileiros Cardiol 2011; 97(4): 350-6.

[59] Liu M, Yu Y, Jiang H, *et al*. Simvastatin suppresses vascular inflammation and atherosclerosis in ApoE(-/-) mice by downregulating the HMGB1-RAGE axis. Acta Pharmacol Sin 2013; 34(6): 830-6.

[60] Brinjikji W, Yong Hong D, Dai D, Schroeder DJ, Kallmes DF, Kadirvel R. Statins are not associated with short-term improved aneurysm healing in a rabbit model of unruptured aneurysms. J Neurointerv Surg 2017; 9(2): 200-3.

[61] Melo AC, Valenca SS, Gitirana LB, *et al*. Redox markers and inflammation are differentially affected by atorvastatin, pravastatin or simvastatin administered before endotoxin-induced acute lung injury. Int Immunopharmacol 2013; 17(1): 57-64.

[62] Manitsopoulos N, Orfanos SE, Kotanidou A, *et al*. Inhibition of HMGCoA reductase by simvastatin protects mice from injurious mechanical ventilation. Respir Res 2015; 16: 24.

[63] Ndrepepa G, Fusaro M, King L, *et al*. Statin pretreatment and presentation patterns in patients with coronary artery disease. Cardiol J 2013; 20(1): 52-8.

[64] Leoncini M, Toso A, Maioli M, *et al*. High-dose atorvastatin on the pharmacodynamic effects of double-dose clopidogrel in patients undergoing percutaneous coronary interventions: The ACHIDO (Atorvastatin and Clopidogrel HIgh DOse in stable patients with residual high platelet activity) study. JACC Cardiovasc Interv 2013; 6(2): 169-79.

[65] O'Brien EC, Simon DN, Roe MT, Wang TY, Peterson ED, Alexander KP. Statin treatment by low-density lipoprotein cholesterol levels in patients with Non-ST-segment elevation myocardial infarction/unstable angina pectoris (from the CRUSADE Registry). Am J Cardiol 2015; 115(12): 1655-60.

[66] Mytas D, Zairis M, Karanasos A, *et al*. Effect of statin pretreatment on the outcome of ST-segment elevation myocardial infarction in patients without prior history of coronary artery disease. Hellenic J Cardiol 2013; 54(6): 422-8.

[67] Aydin MU, Aygul N, Altunkeser BB, Unlu A, Taner A. Comparative effects of high-dose atorvastatin versus moderate-dose rosuvastatin on lipid parameters, oxidized-LDL and inflammatory markers in ST elevation myocardial infarction. Atherosclerosis 2015; 239(2): 439-43.

[68] Liu HL, Yang Y, Yang SL, *et al*. Administration of a loading dose of atorvastatin before percutaneous coronary intervention prevents inflammation and reduces myocardial injury in STEMI patients: a randomized clinical study. Clin Therap 2013; 35(3): 261-72.

[69] Sun F, Yin Z, Shi Q, Zhao B, Wang S. Effect of short-term high-dose atorvastatin on systemic inflammatory response and myocardial ischemic injury in patients with unstable angina pectoris undergoing percutaneous coronary intervention. Chin Med J 2014; 127(21): 3732-7.

[70] Yang J, Liu C, Zhang L, *et al*. Intensive Atorvastatin therapy attenuates the inflammatory responses in monocytes of patients with unstable angina undergoing percutaneous coronary intervention via peroxisome proliferator-activated receptor gamma activation. Inflammation 2015; 38(4): 1415-23.

[71] Li J, Chen H, Ren J, *et al*. Effects of statin on circulating microRNAome and predicted function regulatory network in patients with unstable angina. BMC Med Genom 2015; 8: 12.