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Effects of Statins on Myocarditis: A Review of Underlying Molecular Mechanisms

Negin Parsamanesh[1], Morteza Karami-Zarandi[1], Maciej Banach[2,3*], Peter E. Penson[4], Amirhossein Sahebkar[5,6,7*]

[1]Department of Molecular Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[2]Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, Lodz, Poland
[3]Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland
[4]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK
[5]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[6]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[7]Halal Research Center of IRI, FDA, Tehran, Iran

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***Corresponding Authors:**

Prof. Amirhossein Sahebkar, Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran. Tel: +985138002299; Fax: +985138002287; E-mail: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com

Prof. Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA, Head, Department of Hypertension, Medical University of Lodz, Rzgowska 281/289; 93-338 Lodz, Poland. Phone: +48422711124; E-mail: maciej.banach@iczmp.edu.pl

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ABSTRACT:

Myocarditis refers to the clinical and histological characteristics of a diverse range of inflammatory cellular pathophysiological conditions which result in cardiac dysfunction. Myocarditis is a major cause of mortality in individuals less than 40 years of age and accounts for approximately 20% of cardiovascular disease (CVD) events. Myocarditis contributes to dilated cardiomyopathy in 30% of patients and can progress to cardiac arrest, which has a poor prognosis of <40% survival over 10 years. Myocarditis has also been documented after infection with SARS-CoV-2. The most commonly used lipid-lowering therapies, HMG-CoA reductase inhibitors (statins), decrease CVD-related morbidity and mortality. In addition to their lipid-lowering effects, increasing evidence supports the existence of several additional beneficial, 'pleiotropic' effects of statins. Recently, several studies have indicated that statins may attenuate myocarditis. Statins modify the lipid oxidation, inflammation, immunomodulation, and endothelial activity of the pathophysiology and have been recommended as adjuvant treatment. In this review, we focus on the mechanisms of action of statins and their effects on myocarditis, SARS-CoV-2 and CVD.

Key words: Myocarditis, SARS-CoV-2 , Inflammation, HMG-CoA inhibitors, RhoA.

No. of words: 166

Alphabetical List of Abbreviations:

ACE2	angiotensin-converting enzyme 2
AGEs	advanced glycation end products
AIDS	acquired immunodeficiency syndrome
AIR	autoimmune retinopathy
ALRs	AIM2-like receptors
AngII	angiotensin II
APC	antigen-presenting cell
ARDS	acute respiratory distress syndrome
CAD	coronary artery disease
CAR	adenovirus receptor
CCs	cholesterol crystals
CIITA	class II transactivator
CMV	cytomegalovirus
COVID-19	Coronavirus Disease 2019
CTLs	C-type lectin receptors
CVB	type B Coxsackievirus
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
EAE	experimental autoimmune encephalomyelitis
EAM	experimental autoimmune myocarditis
EBV	Epstein-Barr virus
EM	eosinophilic myocarditis
EMB	endomyocardial biopsy
eNOS	endthotelial nitric oxide synthase
FPP	farnesyl pyrophosphate
GGPP	geranylgeranylpyrophosphate
HAART	highly active antiretroviral therapy
HHV-6	human herpesvirus 6
HIV	human immunodefficiency virus
HLA-II	human leukocyte antigen class II
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HSV	herpes simplex virus
IA	inflammatory arthritis

ICAM1	Intercellular Adhesion Molecule 1
ICU	intensive care unit
IFNγ	interferon gamma
IL	interleukin
iNOS	inducible nitric oxide synthase
LDL-C	low-density lipoprotein cholesterol
LFA1	lymphocyte function-associated antigen-1
LPS	lipopolysaccharide
MAC1	macrophage receptor-1
MCP-1	monocytic chemoattractant protein 1
MHC	major histocompatibility complex
MI	myocardial infarction
NADPH	nicotinamide-adenine dinucleotide phosphate
NLRs	NOD-like receptors
NT-proBNP	N-terminal pro-brain natriuretic peptide
PI3Ks	phosphoinositide 3-kinases
PPAR	peroxisome proliferator-activated receptor
PRRs	pattern recognition receptors
PTKs	protein kinases
RLRs	RIG-I-like receptors
ROCK	Rho-kinase
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TGF-β	transforming growth factor β1
Th	T helper lymphocytes
TLRs	toll-like receptors
TNFα	tumor necrosis factor alfa
tPA	tissue plasminogen activator
VCAM1	vascular cell adhesion molecule 1

Statins in Infectious Diseases

Cholesterol plays a critical underlying role in the development of atherosclerosis and coronary artery disease (1). Following the discovery of the role of cholesterol in cardiovascular disease (CVD) in 1856 (2), many studies confirmed the relationship between high blood cholesterol levels and an increased probability of CVD (3,4). Consequently, cholesterol reduction was identified as one of the main strategies for the treatment and control of CVD (5, 6). The enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase was identified as a rate-limiting enzyme in the biosynthesis of cholesterol (7). In the 1970s, the discovery of mevastatin, a natural inhibitor of HMG-CoA reductase, derived from *Penicillium citrinum* led to clinical trials in which statins were used to reduce circulating concentrations of cholesterol (8,9). Statins suppress the HMG-CoA reductase enzyme which is necessary for cholesterol synthesis and are effective in primary and secondary CVD prevention (10). Many effects of statin treatment have been attributed to decreased levels of serum cholesterol. Even so, statins could also block the synthesis of isoprenoids (lipids essential for the binding of intracellular signaling molecules such as Rho, Rac and Cdc4) by suppressing HMG-CoA reductase (11). In addition, statins have been demonstrated to have activities against bacterial, viral, and fungal infections in both *in vitro* and *in vivo* studies. The course of infection with a wide range of agents has been reported to be affected by statins. These include methicillin-sensitive *Staphylococcus aureus* (12), *Clostridium difficile* (13), *Mycobacterium tuberculosis* (14), *Chlamydophila pneumoniae* (15), *Plasmodium falciparum* (16), *Candida albicans*, *Aspergillusfumigatus* (17), hepatitis C virus (18), Epstein-Barr virus (19) and type B Coxsackievirus (CVB) (20).

Myocarditis is an infectious disease, most commonly caused by Type B Coxsackievirus. The majority of CVB infections are asymptomatic (21). However, at least 70% of the world population is estimated to have anti-Type B Coxsackievirus antibodies. The severity of

symptoms varies from a mild infection to sudden cardiac arrest in young and healthy individuals (20). The exact mechanism by which CVB causes myocarditis is still unclear. Host immunologic factors play a critical role in the pathogenesis of CVB myocarditis. The Fas/FasL system, and Fas-associated apoptosis are major underlying mechanisms for myocarditis (22). Various cell types such as cardiomyocytes, smooth muscle cells, and endothelial cells express Fas, and the binding of Fas to the FasL initiates the production proinflammatory cytokines and subsequent inflammatory responses (20,22). The presence of soluble Fas competitively inhibits FasL-induced apoptosis. Atorvastatin reduces FasL expression in CVB-infected murine myocardial cells and improves cardiac muscle cell function after infection with CVB (20,23). Lovastatin decreases the expression of coxsackie and adenovirus receptor (CAR) by a mechanism which depends on the Rac1/Cdc42 pathway in human endothelial cells (24). Conversely, lovastatin accelerates apoptosis mediated by prostate-restricted replication-competent adenovirus-mediated TRAIL. Lovastatin significantly increases adenovirus binding by the elevation of CAR expression. Depletion of cholesterol and lipid rafts by lovastatin is the proposed mechanism for the increased expression of CAR (25).

Anti-Inflammatory Actions of Statins

Inflammatory responses appear to play an important role in the pathogenesis of CVD, and statins have been demonstrated to exert anti-inflammatory effects (26). As mentioned above, statins have various effects on inflammatory mediators, both dependent and independent of their lipid-lowering effects (27). Statins modify the transcription of inflammatory mediators and alter inflammatory signalling in endothelial cells, smooth-muscle cells, platelets, and native immune system cells such as macrophages and neutrophils (28). Inflammatory mediators such as tumor necrosis factor alfa (TNFα), interleukin (IL) 1β, IL-6, and IL-8 are reduced by the action of statins (6,29). The core function of the endothelium is to provide an

anti-adhesive, antithrombotic surface. Cytokines and hypercholesterolaemia stimulate endothelial dysfunction and result in impaired production of endothelial nitric oxide synthase (eNOS) (30-32). NO mediates several benefits, including vascular relaxation and suppression of smooth-muscle-cell proliferation, leukocyte, or platelet-endothelial interactions and exocytosis (33). Statins alleviate many of the adverse effects of reduced NO availability in the inflammatory environment, and improve endothelial function (34). Although recovery of endothelial function may result from a decrease in low-density lipoprotein cholesterol (LDL-C) levels, multiple studies indicate that endothelial function is restored before major improvements in serum cholesterol concentrations (35). Rosuvastatin increases the production of nitric oxide from the endothelium and downregulates the adhesion and transmigration of leukocytes by endothelial P-selectin in male Sprague-Dawley rats (36). Inflammatory stimuli also induce the expression of vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1) and attract immune cells into the wall of the vessels. Statins suppress the expression of these adhesion molecules and thereby reduce the accumulation of immune cells within the vessel wall and decrease inflammation (37,38). Healthy endothelium expresses thrombomodulin and tissue plasminogen activator (tPA) which reduce the likelihood of coagulation of the blood. The inflammatory response decreases the expression of thrombomodulin and tPA and initiates a pro-coagulant state. Statins induce elevated levels of thrombomodulin and tPA, while reducing expression of tissue-factor, and thus restoring balance within the coagulation system (39) (**Figure 1**).

Lovastatin inhibits leukocyte recruitment during acute inflammation by downregulation of the monocytic chemo attractant protein 1 (MCP-1), IL-6, and RANTES (which is expressed and secreted by normal T-cells) (40,41). Additionally, statins reduce the secretion of MCP1 and interleukin 8. On the other hand the infiltration and recruitment of leukocytes by lymphocyte function-associated antigen-1 (LFA1) and macrophage receptor-1 (MAC1) are key

events during the formation of atherosclerotic lesions (6). Statins directly bind to LFA1 and also attenuate the expression of MAC1 on the monocyte surface (6). Activation of T helper lymphocytes is attenuated by reducing Ca^{2+} influx and IL-2 production in T cells (42). Moreover, the expression of human leukocyte antigen class II (HLA-II), an important molecule for the activation of T helper (Th) lymphocytes is decreased in an interferon gamma (IFNγ) mediated manner by changes to the formation of HLA-II lipid raft. Production of IFNγ is reduced after statin treatment (43) (**Figure 1**). Classification of statins according to their characteristics is presentented in **Table 1.**

Molecular Mechanism of Action

Innate immunity is the body's initial line of protection, and is mediated by receptors (so-called pattern recognition receptors) in response to known antigens (PRRs). These receptors are found in innate immune cells such as neutrophils, macrophages, and other inflammatory cells. There are five classes of PRRs: RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), AIM2-like receptors (ALRs), toll-like receptors (TLRs), and C-type lectin receptors (CTLs) (44, 45). Several of them (CTLs and TLRs) are found on the cell membrane, although some classes are cytoplasmic receptors and are found in the cytoplasmic space (RLRs and NLRs) (46, 47). The PRR-related signaling pathway, particularly TLRs and NLRs, has long been recognized as the link between inflammatory diseases (such as autoimunity and atherosclerosis and the innate immune system. The well-known receptor that recognizes the endogenous threat signal produced by the existence of cholesterol crystals (CCs) is NLR, particularly NLRP3, which triggers the activation of the inflammasome complex (48). The existence of CCs and increased LDL are the key stimulators implicated in atherosclerosis pathogenesis, resulting in inflammasome NLRP3 expression (49).

Statins exert two distinct effects on the molecular pathways within cells leading to anti-inflammarory effects (50,51). The first, and best characterised mechanism of action is on the

pathway responsible for the biosynthesis of cholesterol and isoprenoids, and relies on the prevention of mevalonate biosynthesis, decrease in cholesterol production and upregulation of the low-density lipoprotein receptor gene, which leads to increased hepatic uptake of cholesterol from circulating lipoproteins (52,53). Another mechanism of action is the cholesterol-independent pathway, which involves interfering in the modification of cell signalling proteins. In addition to preventing cholesterol biosynthesis, inhibition of HMG-CoA reductase also reduces the production of isoprenoid intermediates such as farnesyl pyrophosphate (FPP), geranylgeranylpyrophosphate (GGPP), isopentanyl adenosine, polyisoprenoid side chains of ubiquinone, and nuclear lamins (54,55). FPP and GGPP are essential for the post-translational farnesylation and geranylgeranylation of crucial signaling proteins, including the Ras and Rho GTPase family. Indeed, the isoprenylation of RhoA is crucial for the activation of Rho-kinase (ROCK) and subsequent cellular effects (54). ROCKs regulate myosin light chain phosphorylation and alter the function of the actin cytoskeleton. Consequently, the formation of focal adhesion complexes, smooth muscle retraction, cell migration, and gene expression are affected tight and adhering junctions via actin cytoskeletal contractions, moreover ROCKs could also control endothelial cell permeability and macrophage phagocytic activity (27,56). Increased leukocyte ROCK activity is associated with systemic and pulmonary hypertension, metabolic syndrome, dyslipidemia and coronary artery disease (CAD) (57-60). The inhibition of ROCK results in statin-like effects, including limiting cardiac fibrosis, hypertrophy, and myocardial infarction (MI) (27). Statins have the opposite effect to ROCK, independently of their action on LDL-C (27). Myocardial remodelling is a common response to cardiac damage and is induced by angiotensin II (61,62). The Rho/Rac/cdc42 protein family has been demonstrated to participate in the remodelling of the myocardium (63,64). In animal models of cardiac hypertrophy, statins inhibit the geranylgeranylation of Rac1 and can prevent cardiac hypertrophy through the nicotinamide-

adenine dinucleotide phosphate (NADPH) oxidase-dependent reactive oxygen species (ROS) production pathway (38). The guanine nucleotide binding proteins, Rac1 and Rap are necessary for the production of NADPH oxidase-dependent ROS. During excessive pressure, dilation, and Ang II-infusion NADPH oxidase-dependent ROS activated by GTP binds to Rac1 and triggers myocardial remodelling and cardiac hypertrophy (38,63-65).

Another example of a cholesterol-independent pathway by which statins act, is the regulation of eNOS (66). Endothelial NO is crucial for vascular smooth muscle proliferation and interactions of endothelial-leukocytes (67,68). NO facilitates blood flow by stimulating vasodilation, reducing regional hypoxia, and prevents platelet aggregation and subsequent vascular lesions (67). Also, elevated NO levels downregulate P-selectin, VCAM-1, and the expression of ICAM-1 (37,38). Statins alter NO production through multiple mechanisms. RhoA geranylgeranylation is necessary for the inhibition of eNOS. A reduction in RhoA geranylgeranylation results in the overexpression of eNOS and consequently restores function in endothelial cells (69). Also, GGPP can remedy the overexpression of eNOS. In the caveolae, an integral membrane protein named caveolin 1 binds to eNOS and blocks NO production. Statins limit caveolin-1 expression and increase the activity of eNOS (30-32). Statins activate NF-E2-related factor 2 (Nrf2) via the PI3K/Akt pathway, and then suppress the activation of NADPH oxidase, which is a producer of ROS (70-72). A reduction in ROS production and angiotensin II (AngII)–type 1 receptor has been suggested as a means by which statins may have therapeutic potential in hypertension (73). Furthermore, statins reduce ROS production by increasing the expression of the peroxisome proliferator-activated receptor gamma (PPAR-γ) co-activator that is also a major regulator of mitochondrial biogenesis (74). The activation of PPARs by statins ameliorates inflammation provoked by lipopolysaccharide (LPS) (75). This function is independent of cholesterol-lowering mechanisms because, in PPARα-null mice, lipopolysaccharide-related inflammation is not affected by statins (76). The beneficial

effects of simvastatin result from the increased activity of PPAR-γ by simvastatin and, therefore, the inhibited activity of LPS-induced TNF-α and MCP-1 (77). Atorvastatin inhibits cardiac fibrosis-induced advanced glycation end products (AGEs) by triggering PPAR-γ activation. Fibroblast differentiation and proliferation caused by AGEs is based on the AGEs-RAGE-ERK1/2 pathway and atorvastatin was able to stop this mechanism by activating PPAR-γ-gamma induction (78).

Literature Search

Searches were conducted in the major electronic databases, PubMed and EMBASE to find original and review articles, meta-analyses and expert commentaries published (until December 2020) in relation to the role of statins in myocarditis and during the coronavirus infection. The search terms “myocarditis”, “COVID-19” and “coronavirus” were used in combination with “statins”. Related cross-references from these publications were also discussed.

Myocarditis

Myocarditis is the main reason for sudden death in the population under the age of 40, and may account for 15 to 20% of cardiovascular events. In 30% of patients, myocarditis leads to dilated cardiomyopathy, with advancement to cardiac failure - a major source of morbidity and mortality among younger people. Prognosis is poor, with a 10-year life expectancy less than 40% (79). Myocarditis refers to the clinical and histological feature of a wide variety of pathological cardiac inflammatory cellular processes, with or without the involvement of myocyte necrosis (80). For patients with acute and chronic myocarditis, abnormalities in the quantity and activity of lymphocyte subtypes and macrophages are usually observed in addition to antibody-mediated injury (80,81).The immune response in the heart triggers morphological and functional irregularities in cardiac myocytes, which in turn result in global or regional

contractile dysfunction, chamber stiffness, or conduction disorders (81). People with severe myocarditis commonly have non-specific symptoms such as dyspnoea, chest pain, or tachycardia. Severe myocarditis can also cause cardiac injury without symptoms, and the prevalence of chronic dilated cardiomyopathy (DCM) in this situation is unknown. Chronic myocarditis can also cause immune-mediated cardiac injury and disorders (82,83).

Etiology of Myocarditis

Myocarditis can be categorized by clinical criteria, etiology, and histology. Therefore, the treating physician must recognize and use diagnostic and clinical information from each classification.

a. Exposure to Infection

A variety of infections conditions can lead to myocarditis. In North America and Western Europe, viral infection is a major cause, with enterovirus and adenovirus traditionally being the most commonly cited causes (84-86). More recently, the *Parvoviridae* family (B-19) and human herpesvirus 6 (HHV-6) have been the most frequently identified virus genomes in endomyocardial biopsy (EMB) (87). Immunological evidence has linked the hepatitis C virus to myocarditis and DCM, primarily in Japan (87). Pathogens less-commonly associated with myocarditis include herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) (88). Over 25% of cases of myocarditis involve co-infection by two additional viruses (84). Myocarditis and DCM have been linked with the acquired immunodeficiency syndrome (AIDS) (89). While direct myocardial injury from the human immunodifficieny virus (HIV) infection is uncommon, co-infections can trigger cardiomyopathy in individuals infected with HIV (90). Myocarditis was detected in more than half of the patients in studies conducted before the availability of potent antiretroviral treatments (91). The development of powerful anti-retroviral drugs, with substantial immune reconstitution, significantly improved

patient longevity, and the identification of new harmful effects of highly active antiretroviral therapy (HAART) raised the possibility of adverse cardiovascular events in treated patients (92). The probability of HAART-induced atherosclerosis progression, with an elevated risk of coronary incidents is probably the main concern. Insulin resistance and dyslipidemias are a well known consequence of PIs, and huge epidemiological studies are ongoing to quantify cardiovascular risk in patients receiving HAART therapy. Other relevant details will come from trials discussing the problems of endothelial defects and coagulation in patients with HIV+. In order to continually improve longevity and quality of life of HIV patients, a good understanding of drug-related cardiac negative impacts is required. Otherwise, the efficacy of HAART can be undermined by the risks associated with unknown toxicity (92). The frequency of myocarditis among HIV-infected patients living in developing countries has declined substantially since the advent of antiretroviral drugs. However, in developing countries where accessibility to antiretroviral treatment is limited, the rate of myocarditis associated with HIV continues to rise (89). While many bacterial infections may induce myocarditis, bacterial myocarditis is much less prevalent than that caused by viral infections. Clostridium and diphtheria, and associated bacterial toxins can cause serious myocardial lesions (93). Bacteremia from any origin cause myocarditis, with the most common causes being *streptococcus*, *meningococcus*, and *listeria* (93). Chagas' disease, caused by the *Trypanosoma cruzi* protozoa, is widespread in South and Central America and sometimes reported in the United States, and is sometimes identified in cases of severe or chronic cardiomyopathy (94).

b. Systemic and Autoimmune Disorders

Systemic disorders, especially cancer and hypereosinophilic syndrome, as well as helminths (worms) and some enteric protozoa (95), can cause eosinophilic myocarditis (EM) (96-98). EM has been observed in a range of disorders, and following vaccinations for tetanus and smallpox (99). Clinical symptoms of EM include congestive heart failure, rash, coughs,

endocardial and valvular fibrosis. Necrotizing eosinophilic myocarditis is a rare, aggressive form of acute EM with a high incidence of mortality. Idiopathic giant cell myocarditis is a rare, malignant, autoimmune myocarditis which is histopathologically characterized by multinucleated giant cells, myocyte necrosis, and infiltration of inflammatory lymphocytes (100). This condition typically affects young people and is associated with high mortality unless heart transplantation is carried out. Giant cell myocarditis is uncommon in children and adults and is also correlated with immune-mediated disorders in several organs (100,101). Because of its association with several autoimmune diseases and hypersensitivity to drugs, it is considered to be an autoimmune condition (102,103). Unusual ventricular arrhythmias in this condition appear to result from second- or third-degree AV block with chronic DCM and do not respond to standard care (104).

c. Toxins and Hypersensitivity

Drugs may induce myocardial inflammation by specific adverse effects on the cardiovascular system and by precipitating hypersensitivity reactions (105). Anthracycline drugs and cocaine are commonly associated with severe myocarditis. However, other treatments, such as phenytoin, amphetamines, cyclophosphamide, and zidovudine can trigger CV toxicity (106). Drug-induced immune responses can even result in eosinophilic myocarditis, which often reacts to the withdrawal of the offending therapy, although adjuvant steroid treatment is usually required. Several antiseizure, antibiotic, and antipsychotic drugs may be precipitate myocarditis via hypersensitivity reactions (106). So many anticonvulsants and antipsychotics as well as a variety of antibiotics contain drugs used in hypersensitivity myocarditis. In any patient taking either prescription or over-the-counter (OTC) drugs, the risk of drug-induced hypersensitivity myocarditis will be considered, especially if eosinophilia or eosinophilic myocardial infiltration is occurring (107).

d. Myocarditis During the Coronavirus Infection

Coronavirus 2 (SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2), also known as Coronavirus Disease 2019 (COVID-19), was first identified in Wuhan, China in December 2019 and announced a pandemic by the World Health Organization (WHO) in March 2020 (108). COVID-19 presentations are highly varied and occur from asymptomatic inflammation to loss of multiple organs and mortality. Pulmonary intervention, like acute respiratory distress syndrome (ARDS), is the most common clinical symptoms of COVID-19, linked with mortality risk, up to 50% in one series (109). Recent research on the pandemic COVID-19 caused by SARS-CoV-2 infection showed that cardiac damage occurred in up to 30 percent of cases, and was associated with increased severity of disease (110,111). There have been many documented cardiac manifestations, such as acute myocardial infarction, myocarditis, severe heart disease, malignant arrhythmia, and cardiogenic shock (112). Cardiac injury has been found to be linked with more serious COVID-19 disease due to an improvement in cardiac biomarkers including cardiac troponins and has been predictive of the intensive care unit (ICU) entry and death (113). COVID-19 induced viral myocarditis has been documented in numerous case reports and review papers. The process of cardiac injury is poorly understood, which makes management difficult. This injury can be triggered due to viral infection by cytokine storms and systemic inflammation, and is linked to increased C-reactive protein and interleukin-6 inflammation markers (114). Zeng *et al.* reported the first case of COVID-19 complicated with fulminant myocarditis. They demonstrated that the heart is a secondary target organ (after the lungs). Anomalieswere not limited to markers of myocardial injury, but also included functional and structural disruption (115). In addition, the main cause of myocardial damage due to viral infection could be immune-related injury. The sudden decline in pulmonary artery systolic pressure and tricuspid annular plane systolic excursion may show that the course of disease is entering the late stage (116). Guidelines have not been identified

for the diagnosis of COVID-19 myocarditis. According to meta-summary of cases, ECG, cardiac biomarkers and echocardiographic changes were consistent with COVID-19 myocarditis, and the presentation may be serious, contributing to mortality (117). However, there are no clear echocardiographic characteristics in myocarditis, so this helps the physician to rule out other sources of cardiac failure, intracavitary thrombosis, and pericardial effusion. In most cases, no final myocardial biopsy was available, but cardiac magnetic resonance imaging was employed (118).

Several potential theories exist regarding the pathogenesis of COVID-19 myocarditis, such as a direct injury by the spreading virus to cardiomyocytes by attaching to angiotensin-converting enzyme 2 (ACE2) receptors (119,120). Moreover, significant cytokine release disorder by maladaptive response of type 1 and type 2 helper T cells result in severe inflammatory reaction leading to oxygen deprivation and cell death of cardiomyocytes (121). The main immune system reacts to a host infected with COVID-19 by production of IFNs and inflammatory cytokines (122). In the early stages of disease, the stimulate of interferons (the first line of protection against viral infections) is slowed, causing inflammatory cells to begin to multiply and bind to tissue, pulmonary or heart, resulting in extreme inflammation c. Autoimmune system over activation with interferon-mediated stimulation of innate and adaptive immune response (121,123).

However, the data for myocarditis with COVID-19 has been restricted to case reports, complicated by the difficulties of developing a verified diagnosis.

The Potential Role of Statins in Myocarditis

Statins Attenuate Inflammatory Infiltration in the Heart

Statins regulate the upregulation of interferon-γ-induced major histocompatibility complex (MHC) class II in antigen-presenting cells. The downregulation of statin-induced MHC-II reduces Th1 activation and the in vivo secretion of proinflammatory cytokines. Tang et al.

reported that the use of atorvastatin decreases inflammatory infiltration in the heart of mice with experimental autoimmune myocarditis (EAM), and reduces the rate of elevation of cytokines such as TNF-α and IFNγ in the EAM model, thereby attenuating the development of EAM (124).

The predominant effect of simvastatin therapy on the development of myocarditis occurs due to suppression of cross-talk between lymphocytes and antigen presenting cells (APCs). Liu *et al.* studied the immunoregulatory effects of atorvastatin on EAM in rats. They showed that the production of Th2-type cytokines is elevated through processes other than suppression of Th1 (125). Investigations into the immunoregulatory impacts of atorvastatin on EAM indicated that the exact mechanism might well be linked to the dysregulation of the MHC class II Ag activation since the class II transactivator (CIITA) mRNA is silenced (125,126). CIITA is known to be the key regulator of type II expression, and the expression rate of CIITA in a cell is closely associated with class II MHC expression (127). TGF-β, IL-4 and IL-10 are cytokines with immunosuppressive properties that inhibit class II MHC at the level of CIITA transcription. Several infectious agents express MHC class II in order to evade immune cells (125). Unlike professional antigen-presenting cells, such as macrophages, B cells and dendritic cells, that also constitutively represent class II cell surface particles, cardiomyocytes, and other nonprofessional APCs need IFN-γ activation for class II expression (127). It is not clear whether epithelial cells or cardiomyocytes are involved in activating and regulating CD41 T-cells in vivo during inflammation in the heart. The impact of statins on the inflammatory pathway may also include NF-κB mechanisms, for instance, via signaling pathways which involve phosphoinositide 3-kinases (PI3Ks) and protein kinases (PTKs) triggered by mitogens (128). Werner et al. demonstrated that the transcriptional regulation of the CAR by lovastatin may also prevent the coxsackievirus B from spreading in vivo, thus also attenuating the subsequent virus myocarditis (129).

Statins have been shown to selectively prevent leukocyte function antigen-1- mediated adhesion of lymphocytes by binding to a novel regulatory integrin site, thereby inhibiting inflammation *in vivo*. Similar findings have resulted from investigations in models of other autoimmune disorders, including experimental autoimmune encephalomyelitis (EAE) (130), autoimmune retinopathy (AIR) (131) and inflammatory arthritis (IA) (132).

Fluvastatin enhances EAM by suppressing T-cell responses and by blocking Th1-type and inflammatory cytokines by NF-κb inhibition. Nevertheless, statins inhibit NF-κb via the phosphorylation suppression of IκBα (133). Azuma et al. have suggested that fluvastatin reduces the proinflammatory cytokine expression of TNF-a, IL-1 and IL-6. Fluvastatin reduces the synthesis of Th1-type cytokines, such as IL-2 and IFN-g, but does not elevate Th2-type cytokines such as IL-10 and IL-4 (134). IL-6 substantially decreases the number and total collagen production of coronary fibroblasts in adults. Neutralisation of IL-6 decreases the severity of the inflammatory disorder (135). An immunized IL-6–deficient animal model had reduced activity of the innate immune system, associated with a predisposition to myocarditis (136). The levels of expression of proinflammatory, secreted proteins, such as IL-6 and TNF-α, are reduced by rosuvastatin in a BALB/c mouse (2–4 months) model of colitis . This result is in accordance with those from previous studies that have demonstrated that statins suppress IL-6 and TNF-α (134,137).

In addition to the findings that fluvastatin reduces $CD4^+$ T-cell infiltration, it has been shown that fluvastatin decreased the dose-dependent proliferation of myosin-specific T-cells in vitro (130). This outcome is contrary to reports that atorvastatin increases the Th2 response, by silencing Th1 in an experimental study of encephalomyelitis (130). Yokosekiet *et al.* demonstrated thatNF-κB demonstrated a key role in regulating myocardial damage in EAM (138). Pitavastatin has been reported to suppress CD4 + T-cell expansion and Th1 and Th17 responses and to enhance myocarditis in the animal model. Since oral administration is well

tolerated, pitavastatin has potential for the treatment of autoimmune disorders that are mediated by Th1/Th17 (139). Observations of prevalent and substantially increased native T1 and T2 levels in many lupus myocarditis cases challenge the findings of previous studies that apply only to extreme acute coronary failure with lupus myocarditis (140) (**Figure 2**).

Potential Role of Statins in Abnormalities of Electrophysiology.

Atorvastatin was shown to prevent atrial fibrillation by suppressing inflammation of sterile pericarditis in an animal model (141), although the exact mechanisms of this antiarrhythmic effect are unclear (142). Tang *et al.* reported substantial differences in the duration of action potentials in cardiomyocytes under inflammatory conditions between atorvastatin-treated and control mice. They observed that atorvastatin causes notable reductions in potassium circulation, which is linked to CV repolarization (143). Proposed mechanisms include inhibition of T-cell responses and prevention of the Fas/FasL adverse effects of T-lymphocytes (144). Additionally, by controlling the expression of potassium current channels, atorvastatin can influence the basal electrical function. The delayed cardio-depressant influence of either basal or stimulated myocardial activity, which evolves within hours to days, is the direct outcome of the regulation of the Ca^{2+}-independent signaling pathway, inducible isoform of nitric oxide synthase (iNOS) by NO processing. Although statins are already commonly used in the care of patients with diverse cardiovascular problems, new therapeutic roles may emerge from a greater understanding of their impact on CV function, independent of cholesterol synthesis. These points must be further investigated in subsequent studies. Echocardiographic findings indicate that rosuvastatin slows the progression of left ventricular remodeling the development of cardiac failure after myocarditis. It was demonstrated that pretreatment with rosuvastatin in a model of EAM model significantly reduced myocardial apoptosis (145) (**Figure 2**).

Effects of Statins on Apoptosis

The suppression of apoptosis by statins in myocarditis may involve various mechanisms. Beta AR activation causes Rac1 expression, which is necessary for myocyte apoptosis and contributes to JNK stimulation and the mitochondrial pathway of death. The beneficial effects of statins on myocytes may be mediated by the suppression of Rac1-dependent apoptotic cell death (146). In addition, statins can prevent Rho A and then trigger Akt, which leads to their anti-apoptotic activity. Statins reduce Rac 1 expression and free-radical production in a model of cardiomyocyte apoptosis provoked by beta adrenergic receptor activation (147). Wu *et al.* showed that simvastatin reduced up-regulation of TNF-α in antigen presenting cells (148) and ameliorated myocarditis induced by myosin and S2-16 (148). Liu *et al.* reported that the rosuvastatin reduces expression of apoptotic cytokines and caspase-3 (145). In addition, numerous studies have suggested that the processes for statin-induced suppression of cell death include the stimulation of the phosphatidylinositol 3-kinase (PI3K) / protein kinase *B* (AkT) / eNOS signaling pathway, suppression of kinase 3β glycogen synthesis to maintain β-catenin, and antioxidant stress (149,150) (**Table 2**).

Results from in vivo studies indicate that statins are very effective at minimizing the severity of experimental myocarditis in animal studies by multi-level, serial interaction with the T-cell-mediated immune response, an essential mediator of the pathogenesis and maintenance of the disease. Large randomized clinical trials are necessary to determine whether these experimental findings can be translated into medical practice, such that statins could be used to improve the currently unsatisfactory therapeutic approach to the management of myocarditis and inflammatory heart disease.

Protective Role of Statins on SARS-CoV-2-Related Myocarditis

Myocardial injury results from myocardial ischemia and non-ischemic causes, including myocarditis, marked by increased levels of cardiac biomarkers. Previous studies have shown

the incidence of myocarditis using cardiac magnetic resonance imaging in patients with MERS (151). Restricted autopsy reports of COVID-19 showed significant interstitial infiltration in heart muscle of proinflammatory mononuclear cells, suggesting the existence of myocardial inflammation and damage from infection with SARS-CoV-2 (152). The first case of SARS-CoV-2 viral particles in the cardiac and cardiomyocyte necrosis utilizing endomyocardial biopsy was reported by Tavazzi and coworkers (153). Their data indicate that the heart may be directly contaminated with SARS-CoV-2 (154,155). Many cases of myocarditis have been documented after infection with SARS-CoV-2. A 53 year old COVID-19 patient was admitted to ICU with the worsening of cardiac systolic dysfunction. Myocarditis has been diagnosed based on the presense of interstitial edema, diffuse biventricular hypokinesis, circumferential pericardial effusion by MRI, and elevated rates of cardiac biomarkers (high-sensitivity troponin T, creatine kinase-MB) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (154). Five patients (7%) with fatal fulminant myocarditis in combination with circulatory failure and 22 deaths (33%) were due to both myocarditis and respiratory failure in a study of 68 fatal cases with COVID-19 (154,156). Unfortunately, no large-scale studies have identified clear incident rates of myocarditis in COVID-19 patients. The incidence of myocarditis in patients with COVID-19 may be due to direct myocardial SARS-CoV-2 localization and systemic inflammatory responses.

Statins modify the lipid oxidation, inflammation, immunomodulation, and endothelial activity of the pathophysiology involved in COVID-19 (157). In silico results indicate that statin molecules interact with SARS-CoV-2 main protease, indicating a possible inhibitory effect on the replication of viruses (158). In silico results indicate that statin molecules interact with SARS-CoV-2 main protease, indicating a possible inhibitory effect on the replication of viruses (158). Statins have also been recommended as adjuvant treatment for COVID-19 (159). The myopathy associated with COVID-19 can also be increased by statins and its drug-to-drug

association profile should be considered especially when antiretroviral, antiviral and antirheumatic medicines are co-prescribed. A better prognosis for viral diseases is also linked with statins. An improved prognosis was linked with the delivery of statin medication to Chinese patients with COVID-19 after hospitalization (159).

Statins have been found to enhance the expression of ACE2 in the kidneys and heart of rabbits that have a saturated fat diet (160,161). In order to assess the effects of therapy with renin-angiotensin-aldosterone system (RAAS) inhibitors, Ang (1-7) and statins, several clinical trials are now ongoing These therapies increase ACE2, which in turn leads to benefits in COVID-19-related pathologies, such as acute and chronic respiratory disease (160). Thus, therapeutics based on ACE2/CD147 could prevent the attachment of SARS-CoV-2 to its receptors and avoid the invasion of its target cells by the coronavirus, potentially providing a technique for developing anti-SARS-CoV-2 therapies (160). Over-expression of ACE2 receptors could improve subsequent syndromes like myocarditis or encephalopathy in various tissues and cell types. Many clinical trials are ongoing to evaluate therapy for statins, a multifunctional group of medications that could block MyD88 signaling and NF-kB reaction, with several possible uses. This could suppress inflammatory responses in COVID19 cases, which would contribute to better outcomes in the disease (162,163). There is data that down-regulation of NF-kB signaling in mouse models of SARS-CoV infection may improve survival.

Statins have also been documented to negatively regulate toll-like receptor-4 (TLR4) production and subsequent stimulation of the primary response to TLR4-myeloid differentiation (MYD)88-NF-kB signaling cascade, which plays a key role in pathogen detection and activation of the innate immune response to viral diseases (1,2). The risk of myocardial damage and myocarditis in acute stages of COVID-19 can be reduced by counteracting cytokine storms with statins. In addition, statin-mediated anti-inflammatory

effects can also facilitate atherosclerotic plaque stability, thus avoiding plaque collapse and CVD events from occurring (164) (3).

A number of immunotherapies proposed as treatments for SARS-CoV-2 are presently being tested in clinical trials (163).

Conclusions

The interplay between myocarditis and statin therapy has not been specifically studied in humans. However, mounting evidence from *in vivo* research suggests that statins are successful in reducing the severity of myocarditis in laboratory animals by altering the T-cell-mediated immune response that is critically involved in the pathogenesis and maintenance of the disease. To conclude, statins have many impacts on cardiomyocytes and endothelial function, including reduction of inflammation and oxidative stress, which may lead to the lipid-independent pleiotropic effects of statins. It is likely that suppression of inflammatory responses via MyD88 signaling and NF-kB in COVID-19 cases would lead to better patient outcomes. Therapy with statins is a potentially novel and encouraging approach to the treatment of pathologies associated with myocarditis and SARS-CoV-2 (165-168). Randomised controlled trials are needed to determine whether this potential can be exploited in clinical practice.

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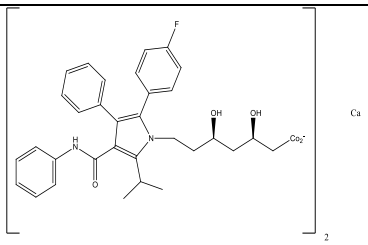
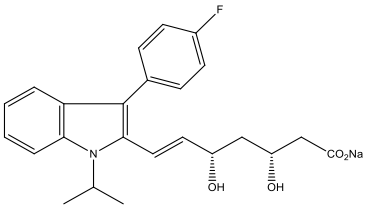
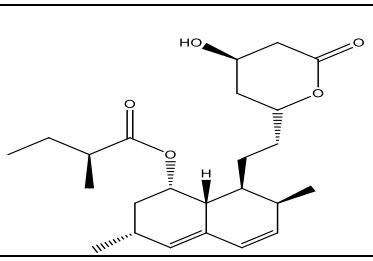
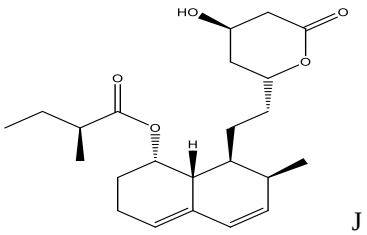
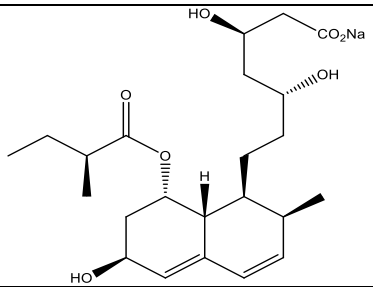
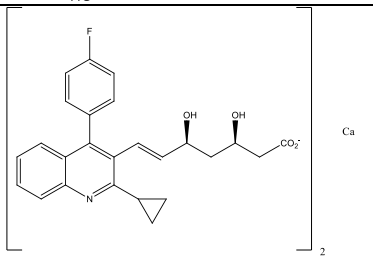
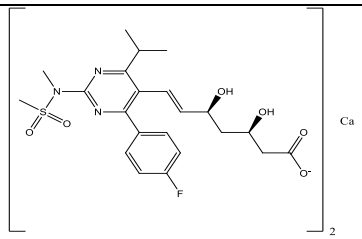
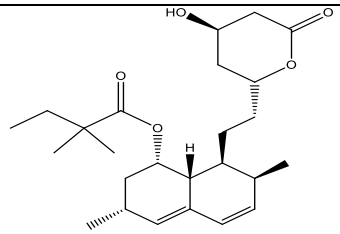
Table 1: Classification of statins according to characteristics				
Name of Statins	**Structure**	**Source**	**Solubility**	**Metabolism**
Atorvastatin		Synthetic	Lipophilic	CYP3A4
Fluvastatin		Synthetic	Lipophilic	CYP2C9
Lovastatin		Natural Derivative	Lipophilic	CYP3A4
Mevastatin		Synthetic	Lipophilic	CYP3A4
Parvastatin		Natural Derivative	Hydrophilic	Restricted CYP3A4
Pivastatin		Synthetic	Lipophilic	Restricted CYP2C9

Rosuvastatin		Synthetic	Hydrophilic	Restricted CYP2C9
Simvastatin		Natural Derivative	Lipophilic	CYP3A4

CYP2C9: Cytochrome P450 2C9, CYP3A4: Cytochrome P450 3A4.

Table 2. Effect of statin treatments on myocarditis				
Drugs	**Experiment model**	**Administration (Daily dose)**	**Outcome**	**Ref.**
Atorvastatin	CVB3-induced myocarditis, mice	5 or 10 mg/Kg oral (2 weeks)	- Upregulated expression of gap junction channel proteins and significant improvement of autoimmune myocarditis -↓ Myocardial expression of Cxs	(165)
	EAM mouse	10 mg/Kg oral (2 weeks)	- ↓ Inflammatory cytokine level - Improves myocardial repolarization - ↓ Outward potassiumcurrent	(124)
	EAM Rat	1 or 10 mg/Kg oral (3 weeks)	-↓ RNA level of type IV CIITA promoter (dosage-dependent) -↑ levels of IFN- γ and IL-2 -↓ levels of IL-4 and IL-10 -↓ MHC class II Ag expression due to silencing of the CIITA mRNA transcription	(125)
	EAM mouse (Lewis rats)	1 or 10 mg/Kg oral (3 weeks)	-↑ the expression levels of Th2 cytokine (IL-4 and IL-10) -↓ the expression levels of Th1 cytokine (IFN-γ and IL-2) - modulating the Th1/Th2 balance	(166)
	CVB3-induced myocarditis, mice	1 or 10 mg/Kg oral (3 weeks)	-↓ myocardial expression and circulating levels of TNFα and IFNγ inhibits apoptosis and Fas expression -↓ histological and functional severity	(20)
Simvastatin	EAM, model	8 mg/Kg oral (45 days)	-↓ co-stimulatory molecule expression (CD28 in lymphocytes,CD80 and CD86 in APCs), -↓ TNF-α production in CD4-positive lymphocytes myocarditic splenocytes and APCs -inhibition of cross-talk between lymphocytes and APCs	(148)
Fluvastatin	EAM, model (Lewis rats)	3.75 or 7.5 mg/Kg oral (3 week)	-↓myosin-induced T cell proliferation suppressing inflammatory cytokines via NFκB -↓ production of Th1-type cytokines (IFN-γ)and (IL-2) and Th2-type (IL-4,IL-10) -↓ infiltration of $CD4^+$ T cells into the myocardium and T cell proliferative responses	(134)
Rosuvastatin	EAM, model	1 or 10 mg/Kg oral (3 weeks)	-ameliorate EAM progression - ↓ apoptosis of cardiomyocytes preserve cardiac output - ↓ the expression levels of TNF-α and IL-6 - ↓ expression of active caspase-3	(145)

Pitavastatin	EAM, model	5 mg/Kg oral (3 weeks)	- ↓ Th1 and Th17 responses - ↓ production of Th1 cytokine IFNγ and Th17 cytokine from autoreactive $CD4^+$ T cells - ↓ the transcription of T-box expressed in T-cells (T-bet) and RORγT - ↓ the phosphorylation of signal transducer and activator of transcription STAT3 and STAT4	(139)

APC: An antigen-presenting cell; *CIITA:* Class II transactivator; CVB3: Coxsackievirus B3; *EAM: Experimental autoimmune myocarditis*; IFNγ: *Interferon* gamma; IL: Interleukin; *MHC*: Major histocompatibility complex; mRNA: Messenger RNA; *NF-κB*:Nuclear factor-*κ*B; RORγT: RAR-related orphan receptor γT; STAT: Signal transducer and activator of transcription; *Th* cells :*T helper* cells; *TNFα:Tumor necrosis factor alpha.*

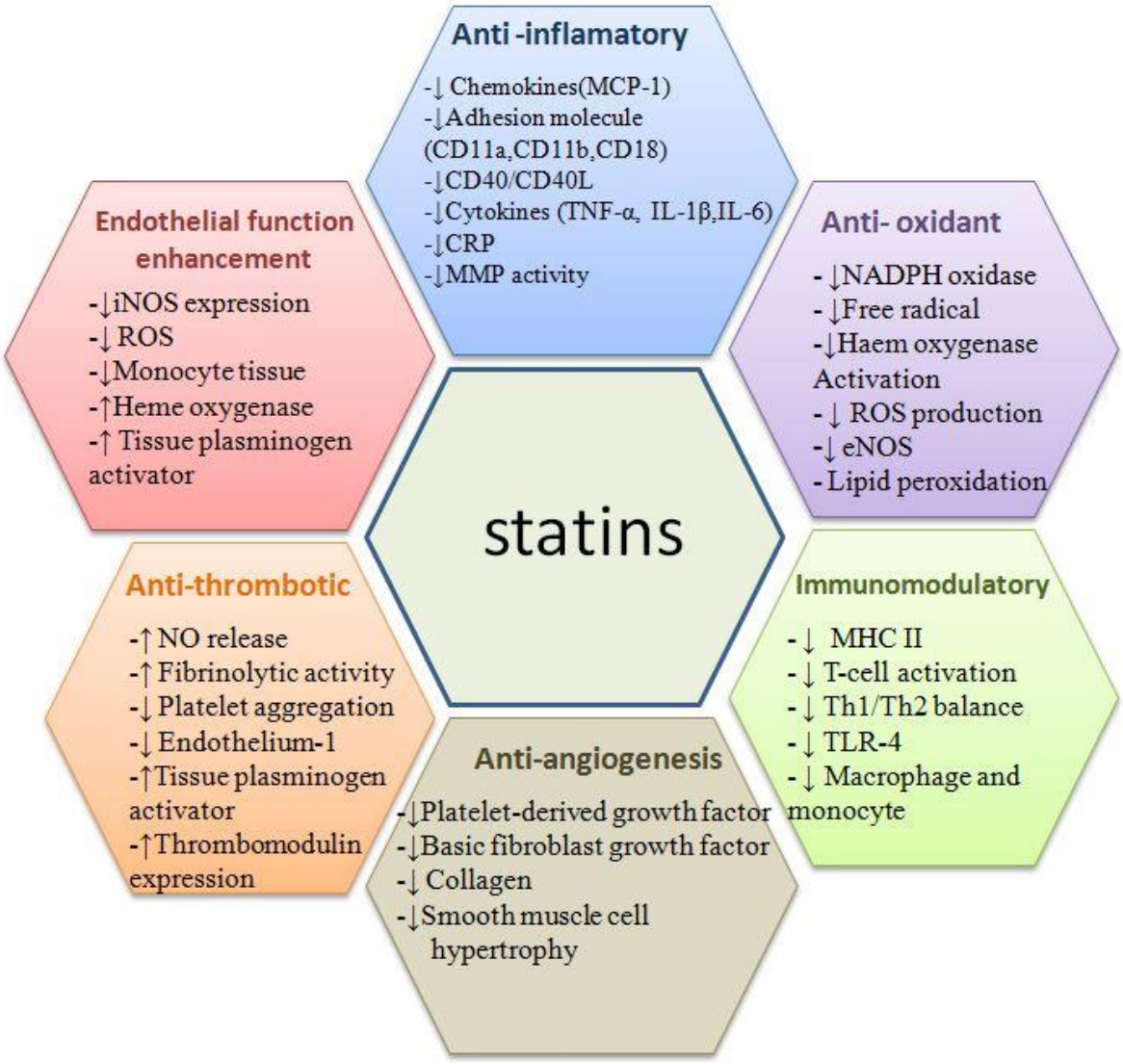


Figure 1. Pleotropic functions of statins.

CRP: *C-reactive protein*; *iNOS* :inducible nitric oxide synthase; MCP-1 :monocyte chemoattractant protein-1; MMPs :Matrix metallopeptidases; *NADPH:* Nicotinamide Adenine Dinucleotide Phosphate Hydrogen; NO: nitric oxide, ROS: *Reactive oxygen species*; Th1:T helper; TLR-4: toll-like receptor-4; *TNF*:*Tumor necrosis factor*.

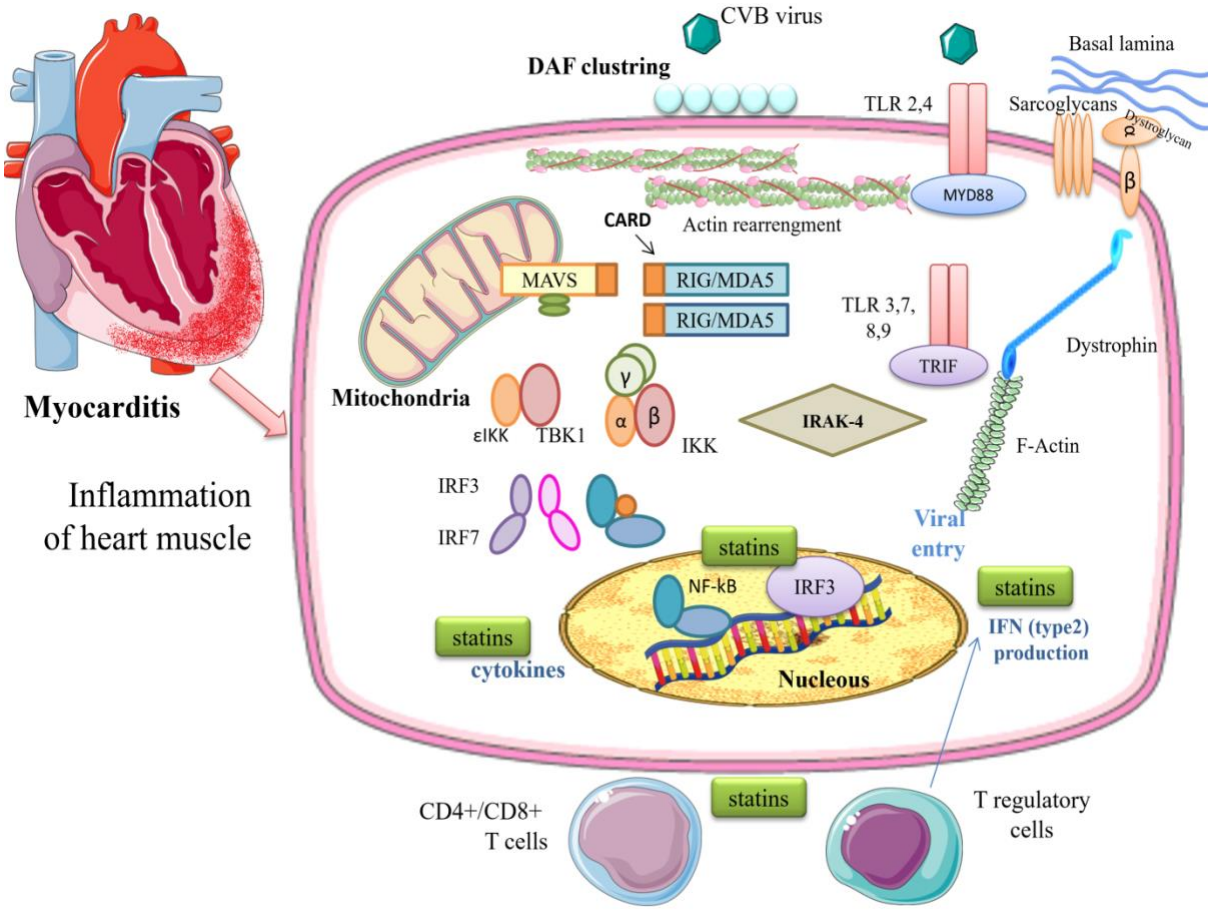


Figure 2. Effects of statins on pathways promoting myocarditis.

CARD: caspase recruitment domains; CVB: Coxsackie B *virus;* DAF: Decay-accelerating factor; IKK:IκB kinase; IRAK-4: interleukin-1 receptor-associated kinase 4; IRF: Interferon regulatory factor; *MAVS*: Mitochondrial antiviral signaling protein; MDA-5:melanoma differentiation associated gene-5; MYD88:Myeloid differentiation primary response 88 ; NF-κB: nuclear factor; TBK1:TANK-binding kinase 1; TLR: toll-like receptors; TNF: tumor necrosis factor; RIG:Retinoic acid-inducible gene I.