Review

Statins: a new insight into their mechanisms of action and consequent pleiotropic effects

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Abstract:

In the recent years, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have emerged as the most important class of lipid-lowering agents. Through inhibition of HMG-CoA reductase, they restrict the rate-limiting step of cholesterol synthesis resulting in up-regulation of low density lipoproteins (LDL) receptors on the cell membrane and reduction of atherogenic LDL consequences. The wide spectrum of non-lipid-mediated pleiotropic effects of statins includes: improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant effects, anti-inflammatory and immunomodulatory properties, stabilization of atherosclerotic plaques and inhibition of cardiac hypertrophy. Several clinical trials have demonstrated and confirmed these beneficial effects of statins in cardiovascular disorders, in primary and secondary prevention settings. Recent studies have reported that the physiological background of the widespread therapeutic efficacy of HMG-CoA reductase inhibitors involved various mechanisms, partially associated with statin impact on posttranslational modifications (e.g. prenylation process). In this review, we have focused on some of them, especially including the statin impact on the endothelial dysfunction and inflammation, peroxisome poliferator-activated receptor (PPAR), beta-adrenergic signaling, renin-angiotensin system and their possible mutual mechanistic linkage.

Key words:
HMG-CoA reductase inhibitors, pleiotropic effects, peroxisome proliferator-activated receptor, beta-adrenergic signaling, renin-angiotensin system, mechanism

Abbreviations: ACE – angiotensin converting enzyme, AMI – acute myocardial infarction, AP-1 – activator protein-1, ApoC-III – apolipoprotein type III, AT_1 – angiotensin II type 1 receptor, β-ARK – beta-adrenergic kinase, CRP – C-reactive protein, CVD – cardiovascular disease, DHA – docosahexaenoic acid, EC – endothelial cell, eNOS – endothelial nitric oxide synthase, ET-1 – endothelin type 1, FA – fatty acids, FPP – farnesylpyrophosphate, GGPP – geranylgeranylpyrophosphate, Gγ3 – G protein gamma subunit, HDL – high density lipoproteins, HMG-CoA – 3-hydroxy-3-methylglutaryl coenzyme A, ICAM-1 – intercellular adhesion molecule type 1, IFN-γ – interferon gamma, IL – interleukin, iNOS – inducible nitric oxide synthase, LDL – low density lipoproteins, LFA-1 – leukocyte function antigen-1, MCP-1 – monocyte chemoattractant protein type 1, MHC-II – Major Histocompatibility Complex class II, MMP – metalloproteinase, NAD(P)H – nicotinamide adenine dinucleotide phosphate, NEFA – non-esterified fatty acid, NF-κB – nuclear factor kappa B, O^-_2 – superoxide anion, PAI-1 – plasminogen activator inhibitor type 1, PPAR – peroxisome proliferation activated receptor, RAS – renin-angiotensin system, ROS – reactive oxygen species, TG – triglycerides, TGF-β – transforming growth factor beta, Th – T helpers, TNF-α – tumor necrosis factor alpha, tPA – tissue plasminogen activator, TXA_2 – thromboxane A_2, VCAM-1 – vascular cell adhesion molecule type 1, VEGF – vascular endothelial growth factor, VLDL – very low density lipoproteins, VSMC – vascular smooth muscle cell

Introduction

In the recent years, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (HMGRI, statins) have emerged as the most important class of lipid lowering agents. Through inhibition of HMG-CoA reductase, they restrict the rate-limiting step of cholesterol synthesis resulting in up-regulation of low density lipoprotein (LDL) receptors on the cell membrane and reduction of atherogenic LDL consequences. Several clinical trials have demonstrated the beneficial effects of statins in cardiovascular disorders, extending beyond their effects on cholesterol level, in primary and secondary prevention settings. As a result, nowadays statins represent one of the most powerful agents for the treatment and prevention of cardiovascular events. Some of the cholesterol-independent or "pleiotropic" beneficial effects of statins include: improvement of endothelial function by the endothelial synthase (eNOS) up-regulation [65, 66], decrease in vascular smooth muscle cell (VSMC) proliferation [67] and macrophage proliferation [1], reduction of platelet activity [44], stabilization of atherosclerotic plaques [33], antioxidant [113], anti-inflammatory and immunomodulatory effects [2, 94].

Many of these pleiotropic effects are mediated by blocking the synthesis of isoprenoid intermediates, with inhibition of small GTP-binding proteins. Members of small GTP-binding proteins: Rho, Ras, Rac, Rap, Ral [118] are important substrates for the post-translational modification by prenylation. Their effectors, protein kinases, transmit extracellular signals into the cells, while prenylation of signal transducers, such as Ras and Rho proteins results in lipid modifications, including covalent addition of either farnesyl or geranylgeranyl isoprenoids to conserved cysteine residues of proteins, needed for the penetration of cell membrane. Statins, *via* inhibition of L-mevalonic pathway, block the synthesis of isoprenoids, including geranylgeranylpyrophosphate, and facilitate accumulation of inactive Rho and Ras in the cytoplasm.

Recent studies have reported that the physiological background of the widespread therapeutic efficacy of HMG-CoA reductase inhibitors involved various mechanisms, partially associated with statin impact on posttranslational modifications (e.g. prenylation process). In this review we have focused on some of them, especially including the statin impact on the endothelial dysfunction and inflammation, peroxisome proliferator-activated receptor (PPAR), beta-adrenergic signaling, renin-angiotensin system and their possible mutual mechanistic linkage. The described below pleiotropic effects of statins are summarized on Fig. 1.

An overview of statin effects on endothelial dysfunction and inflammation

The influence on endothelium is the most widely described of the pleiotropic effects of HMG-CoA reductase inhibitors. It has been generally assumed that cholesterol level reduction by statins is the predominant but not the only mechanism underlying their beneficial effects in endothelial dysfunction and atherogenesis. Statins have been revealed to restore endothelial function *via* the mechanism independent of cholesterol level reduction, which involves, at least partially, the inhibition of Rho isoprenylation resulting in the enhancement of eNOS mRNA stabilization [48]. These effects include statin-induced reduction of the number of inflammatory cells in atherosclerotic lesions and inhibition of adhesion molecules: intercellular adhesion molecule (ICAM-1) [15], vascular cell adhesion molecule (VCAM-1) and E-selectin [89] which are involved in the adhesion/rolling/extravasation of inflammatory cells. Statin administration has also been shown to lower high-sensitivity C-reactive protein (CRP), which is an indicator of a low-grade systemic/vascular inflammation in hypercholesterolemia [92], which is correlated with reduction of coronary events [93].

Early stage of atherogenesis entails leukocyte/endothelial interaction and accumulation of inflammatory cells, and statins were shown to inhibit adhesion of leukocytes to the endothelial cells (EC) [58]. Moreover, HMG-CoA reductase inhibitors regulate the expression of chemokines controlling the migration of leukocytes to subendothelial sites of inflammation, e.g.: monocyte chemoattractant protein-1 (MCP-1) and interleukin type 8 (IL-8) [96]. Matrix metalloproteinases (MMPs) are several matrix-degrading enzymes, which were also described to be implicated in the process of monocyte/macrophage migration, and it has been revealed that statins diminished the expression of some of them [64]. Thus, HMG-CoA reductase inhibitors lower the expression and function
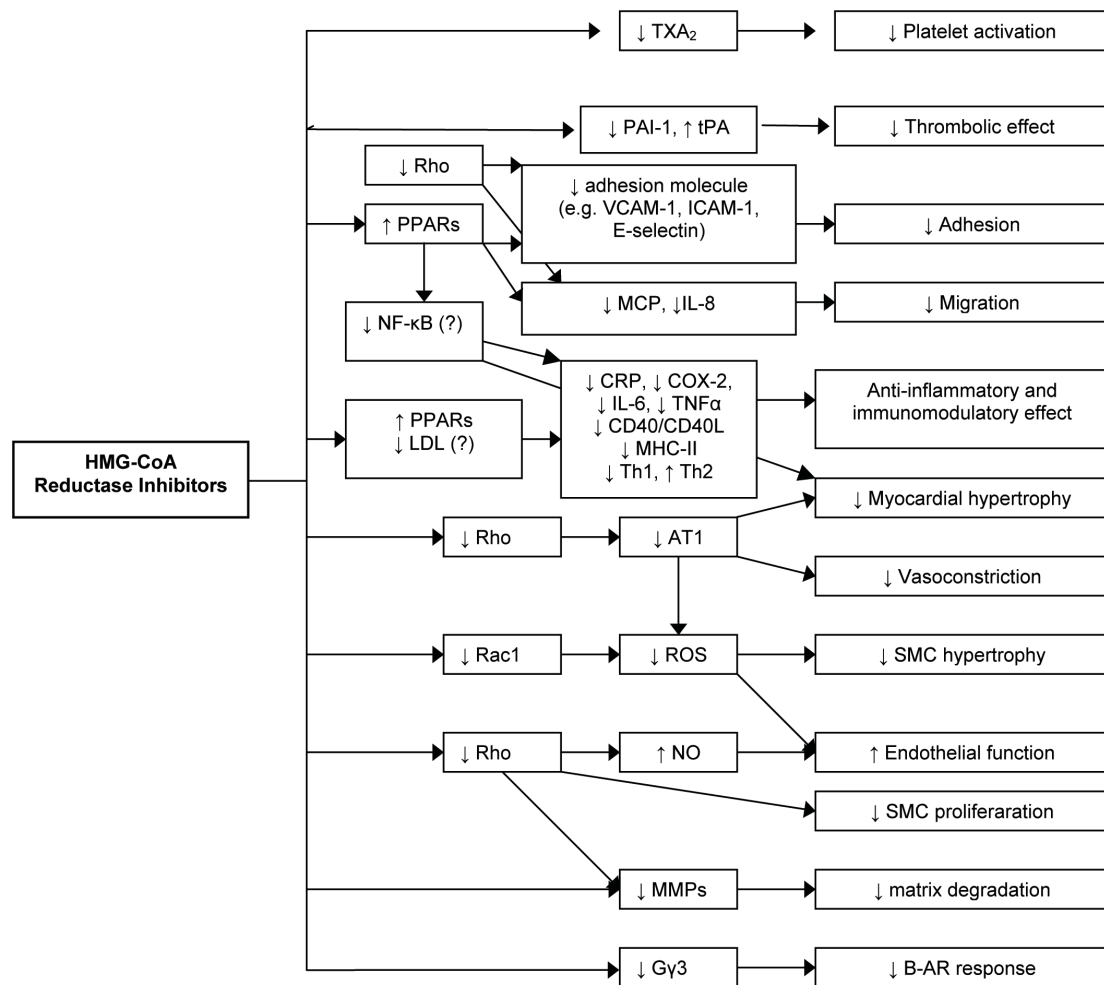
Fig. 1. Pleiotropic effects of statins including prevention of thrombotic responses, improvement of endothelial function, inhibition of migration, adhesion, SMC proliferation and hypertrophy, enhancement of atherosclerotic plaque stability, decrease in oxidative stress and vasoconstriction, attenuation of vascular inflammation, immunomodulatory effect and decrease in beta-adrenergic response. Arrows indicate enhanced ($\uparrow$) or diminished ($\downarrow$) activation/expression of the pathway and/or mediator after statin administration. Abbreviations are defined in the text

of a broad range of MMPs including interstitial collagenases (MMP-1, MMP-13), gelatinases (MMP-2, MMP-9) and stromelysin (MMP-3) [1]. Finally, statins can interfere with the process of rupture of atherosclerotic plaques by modulating lesional procoagulant activity and platelet function. They appear to diminish expression of the major procoagulant tissue factor in macrophages and endothelial cells [29], as well as they promote fibrinolytic activity by diminishing the expression of plasminogen activator inhibitor 1 (PAI-1) and enhancing that of tissue-plasminogen activator (tPA) [9, 27]. Statin impact on platelet function involves also the inhibition of fibrinogen expression and thrombin formation, reduction of platelet aggregation and deposition in diseased vessels, reduction

of cyclooxygenase 2 (COX-2) expression, thromboxane A_2 (TXA_2) and enhanced synthesis of prostacyclin [18].

The molecular mechanism underlying the anti-inflammatory and antiatherogenic processes of statins has not been elucidated yet. However, the above-outlined effects are linked to the signaling pathways of prenylation of small GTP-binding proteins. On the other hand, recent studies have suggested that statins might provide benefit in atherosclerosis by diminishing the activity of nuclear factor kappa B (NF-κB) as well as by modulating the peroxisome proliferator receptors (PPAR), both of which are involved in a wide range of inflammatory pathways and processes that characterize atherogenesis (see below).

Some implications of immunomodulatory properties of statins and their mechanistic background

Some reports revealed that statins may exert beneficial effects on mortality and rejection episodes in cardiac transplant recipients [2], including reduced incidences of cardiac rejection, coronary vasculopathy and increased survival [62, 123]. A randomized double-blind, placebo-controlled study investigating statin efficacy in the treatment of multiple sclerosis is now under way. Recent findings might provide a new insight into beneficial immunomodulatory properties of HMG-CoA reductase inhibitors, including their impact on CD40 signaling, Major Histocompatibility Complex class II (MHC-II) expression and Th2 immune response.

CD40 signaling

The statin impact on CD40-CD40L signaling pathway is another molecular mechanism implicated in the development of atherosclerosis. CD40 signaling, *via* the activation of vascular cells, has been shown to induce inflammatory responses with expression of adhesion molecules and secretion of proinflammatory cytokines, chemokines as well as matrix metalloproteinases [104–107]. Therefore, CD40L, through its receptor CD40, mediates the promotion of formation and progression of atherosclerotic lesions [106]. However, this signaling pathway has been implicated also in the pathogenesis of other chronic disorders e.g. rheumatoid arthritis, multiple sclerosis as well as allograft rejection after organ transplantation.

CD40L is expressed on CD4+ T cells and on activated platelets, and HMG-CoA reductase inhibitors may interfere with CD40/CD40L signaling at several levels. Statins diminish elevated plasma level of soluble CD40L, derived mainly from platelets as well as they diminish the expression of cell-surface CD40L and CD40 on ECs, vascular smooth muscle cells (VSMCs), monocytes, macrophages and T lymphocytes [34]. The described effect, at least partially, may be lipid-lowering dependent. It has been revealed that elevated LDL plasma level and oxidatively-modified LDL augment the expression of CD40L and CD40 on these cells [104]. Consequently, statins by lowering lipids and lipoprotein oxidation might reduce of expression of CD40/CD40L stimulators (e.g. modified lipids, cytokines, growth factors). Interestingly, total cholesterol and LDL plasma levels tend to correlate with soluble CD40L concentrations [34]. Of clinical relevance is the fact that patients with unstable angina have higher concentrations of soluble CD40 ligand than those with stable angina or healthy volunteers, and the elevated baseline plasma CD40L concentrations significantly increase risk of future cardiovascular events [106]. In the large prospective Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, atorvastatin alleviated the risk of recurrent cardiovascular events in patients with acute coronary syndromes only in the presence of high sCD40L levels, and it has been suggested that early statin therapy after acute coronary syndromes countered the risk associated with the elevated sCD40L [59].

Interestingly, PPARγ ligands, such as rosiglitazone and troglitazone, were shown to block platelet surface expression and release of soluble CD40L, and also this molecular pathway seems to contribute to anti-inflammatory and immunomodulatory effects of this class of drugs. However, the above hypothesis requires further molecular studies. On the other hand, the reduction of cytokine-induced CD40/CD40L expression probably is connected also with other signaling pathways, including NF-κB [119].

Major Histocompatibility Complex class II

Major Histocompatibility Complex class II (MHC-II) molecules are expressed on the surface of specialized antigen-presenting cells and are directly involved in the control of the immune response; they are responsible for rejection after organ transplantation [72]. Only limited number of cells express MHC-II constitutively, other cells become MHC-II positive upon induction by the inflammatory mediator, interferon gamma (IFN-γ). It has been reported that statins may regulate IFN-γ-induced MHC-II expression on antigen-presenting cells, and as a result they reduce T-lymphocyte activation. Therefore, HMG-CoA reductase inhibitors are suggested to elicit an immunosupressive effect, and to have numerous other practical clinical applications involving not only organ transplantations but also autoimmune diseases, type 1 diabetes, multiple sclerosis and rheumatoid arthritis. The possible immunomodulatory benefits of statins might also be the consequence of the inhibition of the prenylation pathways. in the presence of L-mevalona-

te, statins appear to abolish the expression of MHC-II [72]. However, further clinical trials are required to confirm these findings. Another point is that, independently of statin effects on MHC-II, HMG-CoA reductase inhibitors have been shown to selectively block the β-2 integrin and leukocyte function antigen-1 (LFA-1). LFA-1 is constitutively expressed in an inactive state on the surface of leukocytes, and in response to several stimuli (e.g. T-cell receptor crosslinking with MHC-II complex), LFA-1 binds to ICAM-1 providing a potent co-stimulatory signal for activated T cells [26].

Interestingly, it has been shown that this inhibitory effect of statins on LFA-1 is unrelated to the inhibition of HMG-CoA reductase and results from binding to a novel allosteric site within LFA-1 [122]. This effect was confirmed for lovastatin, namely, the inhibition of LFA-1 function with stabilization of the receptor in an inactive conformation was observed [122].

Th2 immune response

The immune response might be regulated by statins also *via* T helpers (Th) cells – cytokines pathway. Th2 cells secrete cytokines, e.g. interleukin IL-4, -5, -10, transforming growth factor beta (TGF-β). They were shown to have antiatherogenic properties. Th1 cells mediate proinflammatory cellular immunity by secreting cytokines, e.g. IL-2, IL-12 and tumor necrosis factor alpha (TNF-α) [125]. It has been reported that statins might regulate Th1/Th2 balance [2] and these findings could indicate another mechanistic pathway implicated in beneficial effects of statins. Some *in vivo* and *in vitro* studies have confirmed this hypothesis. In a murine model of autoimmune encephalomyelitis, atorvastatin induced the secretion of Th2 and suppressed the secretion of pro-atherogenic Th1. Studies have revealed that HMG-CoA reductase inhibitors, without any effect on Th2, reduced Th1 suggesting that statin impact on Th1 may be one of the mechanisms providing their beneficial properties in recovery after acute myocardial infarction (AMI) [12].

Hakamada et al. [42] showed that four statins: cerivastatin, simvastatin, lovastatin and atorvastatin augemented Th2 and suppressed Th1 development. The observed effect was completely abrogated by the addition of mevalonate. It has been suggested that the mevalonate pathway should not be excluded considering the mechanistic background of those immunomodulatory effects [42]. Dunn et al. [25] confirmed

the above hypothesis showing that Th2 development was promoted by atorvastatin-induced inhibition of Ras and RhoA prenylation [25]. Another point is that NF-κB preferentially promotes Th1 development [3]. Taking into consideration the statin inhibitory impact on activation of NF-κB, it is also possible that statins inhibit Th1 development *via* attenuation of NF-κB signaling [42]. However, additional research is required to elucidate the mechanisms involved in the statin impact on Th1/Th2 balance.

Peroxisome proliferator-activated Receptor and the pharmacological consequence of its activation

The peroxisome is an organelle of eukaryotic cells, which contains enzymes, such as catalase and oxidase, responsible for the β-oxidation of fatty acids (FA). Peroxisome proliferator-activated receptor (PPAR) is a member of the nuclear steroid-hormone receptor superfamily [52]. Three isoforms of PPAR have been identified. PPARα is mainly expressed in tissues with active fatty acid metabolism, including liver, kidney, brown fat as well as myocardium, skeletal muscles and vascular smooth muscle with endothelium. PPARγ is expressed in adipose tissue, smooth muscle, macrophages and regulates the action of insulin, while PPARδ is distributed in most tissues of the body. PPAR isoforms vary also in their selectivity and sensitivity, therefore, they regulate different sets of genes and there are different pharmacological consequences of PPAR isoform stimulation. All PPARs play a key role as regulators of energy homeostasis by regulating genes involved in fatty acid uptake as well as they parcipitate in the regulation of inflammation [112]. In particular, PPARα regulates vascular function, PPARγ – glucose homeostasis and PPARδ – macrophage lipid homeostasis.

Peroxisome proliferation is a pleiotropic cellular response to a range of chemical compounds (e.g. phthalate, herbicides, leukotriene antagonists), and to certain pathophysiological conditions. It leads to changes in the cellular morphology and enzymatic activity [108]. PPAR isoforms are also activated by fatty acids and fatty acid-derived eicosanoids. Docosahexaenoic acid (DHA) is a natural endogenous ligand of PPARα. Also some drugs were shown to activate

PPARs, e.g. fibrates (PPARα) or their structural analogs – antidiabetic agents: thiazolidinediones (PPARγ) [112].

Fibrates (e.g. fenofibrate) are hypolipemic agents being ligands/activators of PPARα. Some pharmacological properties of fibrates are the consequences of PPAR activation. Activation of PPARα, *via* potentiation of the hepatic fatty acid oxidation in the liver, heart or kidney, leads to increase in expression of lipoprotein lipase, decrease in expression of hepatic apolipoprotein type III (ApoC-III) and decrease in availability of FA for triglyceride (TG) synthesis. As a result, the reduction of triglycerides in chylomicrones and very low density lipoprotein (VLDL) is observed [35], with additional increase in high density lipoprotein (HDL) level [13]. Thereby, fibrates, by activating PPARα, are effective in the clinical management of atherogenic dyslipidemias involving reduced HDL levels. Fibrate-induced activation of PPARα, except for a direct impact on the lipid profile, becomes a physiological background of additional, beneficial effect on cardiovascular disease (CVD). These pleiotropic effects of fibrates as PPAR agonists, include, discussed recently, influence on hypertension, inflammation, vascular dysfunction and remodeling. It has been demonstrated that fibrates could inhibit inflammatory response genes, leading to the inhibition of thrombin-induced production of endothelin-1 (ET-1) in the arterial endothelium [22], decreased production of an inflammatory mediator: IL-6 or cyclooxygenase-2 (COX-2) and down-regulation of the inducible nitric oxide synthase (iNOS) in macrophages [31]. In the liver, fibrate-induced PPARα activation leads to a decrease in C-reactive protein (CRP) expression [61] and IL-6-stimulated fibrinogen expression [36]. Moreover, anti-inflammatory effects resulting from PPAR activation involve a decrease in expression of vascular cell adhesion molecule-1 (VCAM-1), another factor associated with atherosclerotic plaque formation. Additionally, fibrates as PPARα agonists appear to improve endothelial function by the increased expression and release of NO from vascular endothelial cell [11, 39].

Pleiotropic effects of statins mediated by PPARs pathway

Recent studies have revealed that also HMG-CoA reductase inhibitors could act *via* mechanisms involving PPAR pathway. According to the present knowledge, statins exert two different effects on PPARs. HMGRIs increase PPARα expression, as reported in *in vitro* [50] and in *in vivo* [95] studies, and increase PPARα transcriptional activity [51].

In *in vitro* studies, Inoue et al. [50] examined the effects of four statins: simvastatin, pravastatin, fluvastatin and cerivastatin on PPARα and PPARγ isoforms in cultured hepatocytes and endothelial cells. They demonstrated that these agents increased both PPARα expression and its protein levels [50]. Since this isoform is related to the development of inflammation, anti-inflammatory properties of HMG-CoA reductase inhibitors seem to be at least partially the consequence of statin impact on the cellular activity of PPARα. The proposed mechanism may involve the link between PPAR activation, Rho-signaling pathway and posttranslational modifications. Martin et al. [74] noted that incubation of cultured cells with HMG-CoA reductase inhibitors reduced the phosphorylation state of PPARα and increased its transcriptional activity.

In further studies, Inoue et al. [51] attempted to determine whether statins: cerivastatin, fluvastatin and pitavastatin were ligands for PPAR isoforms. The examined drugs were not found to be ligands of PPAR isoforms, although they induced their transcriptional activation. However, the mechanism involved in this effect has remained unknown. Additionally, these drugs were shown to increase, in a dose-dependent manner, the transcriptional activation of PPARα induced by bezafibrate, being a ligand for PPAR. Interestingly, this effect was decreased by the addition of mevalonate, farnesol, geranylgeraniol or cholesterol, which seems to confirm the linkage between PPAR and small G proteins pathway [51].

Both HMGRIs and cellular PPARα activation elicit anti-inflammatory effects characterizing both fibrates and statins. However, similarly to PPARα isoform, PPARγ has been reported to be present in endothelium [55] and atherosclerotic plaques [91]. The activators of PPARγ are troglitazone, rosiglitazone and pioglitazone. These agents have been shown to inhibit proliferation and migration of vascular smooth muscle cells (VSMC) [68]. VSMC proliferation is involved in vascular injury, restenosis and atherosclerosis. Their mechanism of action involves inhibition of many factors associated with degeneration of endothelium, such as activator protein-1 (AP-1), nuclear factor kappa B (NF-κB), tumor necrosis factor alfa (TNF-α), inter-

leukins IL-6, IL-1β, iNOS, metalloproteinase-9 (MMP-9) and others. Recent studies have revealed that positive impact of statins on inflammatory process as well as on the plaque regression and stabilization may be also PPARγ-mediated. It has been shown that atorvastatin and pravastatin activated PPARγ, with an increase in PPARγ levels [41, 126].

Additionally, the combined administration of simvastatin and PPARγ agonists resulted from additive effects on atherosclerotic plaque regression [17].

The above-described pleiotropic effects, characterizing both statins and fibrates and resulting from PPARs activation may involve not only vascular endothelium. Interestingly, studies have demonstrated the impact of statins on PPARα expression not only in endothelial cells. As described above, PPARα regulates multiple enzymes and apolipoproteins implicated in lipid and lipoprotein metabolism. PPARα activation results in the increase in hepatic fatty acid uptake, stimulates the conversion of fatty acids into Acyl-CoA and increases beta-oxidation of fatty acids, which decreases the availability of fatty acids for triglyceride synthesis. Roglans et al. [95] confirmed in *in vivo* studies that the treatment with atorvastatin increased hepatic PPARα mRNA levels and the observed effect was dose-dependent. This effects based on PPARα activation were connected with more than 40% decrease in the hepatic triglyceride content. Another point is that old age strongly reduces the expression and activity of liver PPARα, which could partially explain the age-related increased risk of polymetabolic syndrome with dyslipidaemia, leptin-resistance associated obesity and progressive failure of insulin-mediated glucose metabolism. Interestingly, Sanguino et al. [102] demonstrated that atorvastatin administration to old male rats prevented age-related metabolic changes associated with the reduction of PPARα expression and activity. Moreover, the authors noted statin-induced reduction of plasma non-esterified fatty acid (NEFA) concentration which is suggested to be the main marker associated with insulin resistance syndrome. As the authors concluded, these results confirmed that hypolipemic activity of statins was the consequence of both limited cholesterol availability and cross talk with PPARα. Moreover, the statin lower NEFA what might indicate that these agents are useful in the treatment of a variety of chronic metabolic diseases resulting in elevated plasma NEFA level.

PPARs and hypertrophic changes in myocardium

PPARα isoform is expressed also in the myocardium. It regulates cardiac energy and lipid metabolism and by activating carnitine palmityltransferase transcription, it plays an important role in mitochondrial fatty acid beta-oxidation, critical for fuel generation in the heart [10]. During cardiac hypertrophy, PPARα is inhibited [6], which results in the reduction of cardiomyocyte capacity to metabolize myocardial lipids and accumulate intracellular fat. Moreover, deactivation of cardiac PPARα may be associated with some structural and functional changes in myocardium [38], with contraction band necrosis, inflammatory infiltrates and diffuse fibrosis [121]. Animal studies revealed that PPARα activation prevented myocardial fibrosis induced by angiotensin II [23] and mineralocorticoids [47]. However, strict mechanism linking PPARs and cardiac hypertrophy remains unclear. It is known that depressed myocardial fatty acid metabolism is one of the factors participating in ventricular hypertrophy [99]. It has been suggested that deactivation of PPAR led to cardiomyocyte growth [56], *via* some metabolic cell derangements and stimulation of transcription factors: activator protein-1 (AP-1) and NF-κB needed for the hypertrophic response of cardiomyocytes [85]. Interestingly, recent studies revealed the association between NF-κB signaling pathway, PPARα and statins.

In contrast to PPARα isoform, the role of PPARγ in the heart is less clear. Myocardium is characterized by very low expression of PPARγ [57]. Moreover, the hypertrophic heart experiences an increased glucose utilization and decreased fatty acid oxidation. It is unclear whether PPARγ influences fatty acid metabolism in a similar way to PPARα. It has been suggested that PPARγ may attenuate cardiac remodeling *via* signaling pathway not involved in the control of lipid metabolism [103]. Recent studies revealed that PPARγ activators (e.g. troglitazone) inhibited cardiac hypertrophy induced by angiotensin II or phenylephrine, and it was connected with antagonizing trascription factors-NF-κB activity. It has been suggested that also PPARγ pathway may regulate molecular response to hypertrophic stimuli in the heart [124]. Statins display PPARγ-mediated positive vascular effects. In contrast, it still remains unclear whether

statins, *via* PPARγ activation, prevent negative cardiac changes.

Nuclear factor kappa B (NF-κB) and its possible implication in statin pleiotropy

Nuclear factor kappa B (NF-κB) is a transcription factor that is activated in response to inflammatory stimuli, such as cytokines (e.g. IL1-β, TNF-α). Upon stimulation, NF-κB enters the nucleus where it can induce inflammatory genes [109]. NF-κB is known as a key mediator in atherosclerosis [117], and most pro-inflammatory genes expressed in endothelial cells in response to inflammatory mediators are dependent on this factor [20]. Some reports have demonstrated that atorvastatin and lovastatin reduced proinflammatory cytokine and chemokine expression in smooth muscle cells and mononuclear cells and it was mediated by inhibition of NF-κB activity [84]. Moreover, the above-discussed, statin impact on PPARγ activity was accompanied by abolishment of NF-κB activity [41, 126].

Another point is that activation of NF-κB signaling pathway is one of the most important signal transduction pathways involved in hypertrophic growth of myocardium. Interestingly, NF-κB activation may suppress the activity of PPARs, linking cardiac hypertrophy development and impairment of fatty acid oxidation in myocardium [86]. Thus, a decreased activation of nuclear factor NF-κB could lead to the suppression of PPARs activity and improve prevention or inhibit cardiac hypertrophy development [51].

Additionally, the above linkage between statins and NF-κB in mediating cardiac hypertrophy has been confirmed by Planavila et al. [86]. Cardiac hypertrophy development was inhibited by statin administration and was connected with HMGRI-induced lack of NF-κB activation. These findings seem to indicate that statins play a beneficial role in cardiac hypertrophy not only by reducing the generation of reactive oxygen species.

As described above, statin-induced inhibition of NF-κB is also a possible molecular pathway underlying their beneficial anti-inflammatory and immunomodulatory effects, including impact on Th1/Th2 balance [42] and CD40/CD40L signaling [119].

Large G proteins, beta-adrenergic signaling and statins – another molecular mechanistic linkage?

The physiological background of cholesterol-independent pleiotropic effects of HMG-CoA reductase inhibitors consists in reduction of small guanosine triphosphate (GTP)-binding regulatory proteins, resulting from the blockade of farnesyl pyrophosphate production. These G proteins, such as Rho, Ras, Rac, act as molecular switches, transducing a variety of extracellular signals, promoting cell survival, growth and attenuating apoptosis [16, 71]. Beneficial effects mediated by the above mechanisms include: improvement of endothelial function by the eNOS up-regulation [65], decrease in VSMC proliferation [67] and macrophage proliferation [1], reduction of platelet activity [44], stabilization of atherosclerotic plaque [33], and antioxidant [113] and anti-inflammatory effects [94]. Some of the cholesterol-independent "pleiotropic" effects of statins involve improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation. Inhibition of Rho protein is the main mechanism mediating pleiotropic effects of statins in vascular wall, as Rho is a major target of geranylgeranylation. It performs specific functions, like implication in the regulation of cell shape, motility, secretion or proliferation [116]. Moreover, small G proteins Rho and Ras were shown to be the most extensively investigated molecules in the cardiovascular system [5]. For example small G protein RhoA displays a negative regulatory effect on eNOS gene expression by destabilizing eNOS mRNA [28]. Activation of Rac1 under pathological conditions produces reactive oxygen species (ROS), such as superoxide anion ($O^{\bullet-}_2$), which reacts with NO to generate a potent oxidant, peroxynitrate ($OONO^-$) [5]. Rho induces VSMC proliferation and an enhanced Rho activity may also contribute to the vascular remodeling [110].

However, very recent studies have revealed that statins might also affect isoprenylation of Gγ subunits of the large, heterotrimeric G-proteins, with some functional consequences [76]. G-protein is a crucial binding protein in the interaction of the β-adrenoreceptor with the adenylate cyclase effectors and cAMP formation. β-Adrenoreceptor is regulated *via* coupling to Gs protein and adenylate cyclase activity is stimulated by Gsα subunit. In its inactive form, Gsα

subunit is coupled with guanosine diphosphate (GDP). After the agonist action on the β-adrenoreceptor, Gsα subunit exchanges GDP for GTP, separates from Gβ and Gγ subunits and interacts with adenylate cyclase, which when activated, forms cAMP. Gγ subunits require isoprenylation process for their signal transducing activity. βγ dimers with unprenylated γ subunits cannot activate effectors, e.g. β-adrenergic kinase (β-ARK) [78]. β-ARK phosphorylates β-adrenoreceptor, causing its internalization and desensitization [79]. In a very recent study, Mühlhäuser et al. [76] have reported that atorvastatin caused a decrease in isoprenylation and membrane anchorage of Gγ3 and reduced Gαs subunit content in cultured cardiac myocytes. As a result, G-protein subunits could not attach to the membrane to start signal transduction cascade and β-adrenergic responsiveness of cardiac myocytes was reduced. β-adrenergic-Gαs-adenyl cyclase pathway is associated with regulation of cardiac contractile function. Thus, a functional consequence of interaction was the reduction of the positive inotropic effect of isoprenaline, a β-adrenoreceptor agonist by 30–50% in a concentration dependent-manner. The effect of atorvastatin was completely reversed by mevalonate confirming the association between isoprenylation process and beta-adrenergic activity. Since it is not known whether the changes in G-protein signaling may result from clinically relevant doses of the drug, further studies are needed. However, other studies revealed that atorvastatin at 40 mg reduced Rho isoprenylation in peripheral mononuclear blood cells in healthy volunteers [76].

Nette et al. [79] observed in cardiac surgery patients treated with simvastatin and metoprolol that simvastatin administration prevented metoprolol-induced increase in β-adrenoreceptor density. Additionally, patients receiving simvastatin and metoprolol needed significantly more catecholamine as compared to patients receiving metoprolol alone. The authors concluded that due to metoprolol-induced β-adrenoreceptor up-regulation, statin therapy attenuated hemodynamic stability under β-blockade, and it resulted from statin-induced impairment of β-adrenoreceptor signaling [79]. As mentioned above, statins reduced prenylation of βγ subunits of G-protein, with impairment of receptor density regulation by β-ARK.

Interestingly, an impact on myocyte apoptosis is another link between statins and β-adrenergic receptor. It has been shown that β-adrenergic receptor stimulation in cardiac myocytes results in apoptosis and

is mediated by ROS-dependent activation [90]. It was revealed that β-adrenergic receptor-induced apoptosis required small G protein: Rac1 and that statins inhibited βAR-mediated apoptosis *via* inhibition of βAR-stimulated Rac1 activation [53].

AT$_1$ receptor expression and HMG - CoA reductase inhibitors

Angiotensin II type 1 (AT$_1$) receptor is implicated in cardiovascular pathophysiology, mediating many biological effects of the renin-angiotensin system including vasoconstriction, cell growth, water and electrolyte homeostasis, and sympathetic activation [40]. Overexpression of AT$_1$ leads to the profound increase in angiotensin II-induced pathophysiological changes. Numerous trials revealed that angiotensin AT$_1$ receptor is overexpressed in hypercholesterolemia [83, 114]. Elevated LDL plasma level is a major risk factor of the development of coronary heart disease. Also additional interactions between elevated serum levels of LDL and renin-angiotensin system are potentially important in the pathogenesis of chronic vascular diseases. LDL and oxidized LDL has been associated with impairments of NO release, endothelial function, blood coagulation, cytokine release and enhancement in vascular growth factor efficacy [97]. Moreover, it is known that hypercholesterolemia induced AT$_1$ receptor overexpression. Nickenig et al. [83] demonstrated that stimulation with native LDL led to up-regulation of AT$_1$ gene expression in human VSMC. They showed that LDL markedly elevated AT$_1$ receptor mRNA and protein levels. Also *in vivo* studies confirmed the link between elevated plasma LDL level and AT$_1$ density. As shown by Nickenig et al. [80] in hypercholesterolemic patients with mean LDL 215 mg/dl, AT$_1$ receptor density was 2–3 fold higher as compared to normocholesterolemic subjects (mean LDL 100 mg/dl). Moreover, a statistically significant correlation between AT$_1$ receptor density and LDL plasma concentrations has been demonstrated.

Angiotensin converting enzyme (ACE) was shown to be localized in atherosclerotic lesions. It has been suggested that in hyperlipidemic environment, ACE displayed the capacity of local generation of angiotensin II, another factor promoting development of atherosclerosis [24, 32]. In addition, Daugherty et al.

[19] revealed that hypercholesterolemia greatly increased angiotensin II peptide concentrations.

It is already known that statins down-regulate AT_1 receptor expression. As *in vitro* and *in vivo* [80, 82, 120] studies showed, HMGRIs reduced AT_1 receptor density, however, this effect was not strictly correlated with the changes in cholesterol levels. Statins reduced AT_1 receptor density to 26% of the pretreatment level, but LDL level only decreased to 70% of the primary values [80]. Thus, it has been suggested that the observed beneficial effect of statins was not attributed to their cholesterol-lowering properties, as they are independent of plasma LDL level. Also Wassmann et al. [120] revealed that atorvastatin induced down-regulation of AT_1 gene expression. The physiological background of the observed changes is not strictly clear but the potential statin impact on AT_1 was suggested to be mediated by impaired geranylgeranylation process, resulting from inhibition of mevalonate pathway by HMG-CoA reductase inhibitors. It is known that AT_1 gene expression is regulated predominantly by post-transcriptional modulation [81–83] and the isoprenoid intermediates are important for the post-translational modification and functions of the numerous proteins such as small GTP-binding proteins [66]. The above hypothesis was confirmed by Ichiki et al. [45]. They examined the effects of cerivastatin on AT_1 receptor expression in the presence of two isoprenoids derived form mevalonate: geranylgeranylpyrophosphate (GGPP) and farnesylpyrophosphate (FPP). GGPP, but not FPP was able to prevent cerivastatin-induced AT_1 receptor expression down-regulation. Since the blockade of geranylgeranylation process inhibits the Rho activity, the association between AT_1 receptor expression and Rho expression was also examined. Overexpression of dominant-negative Rho A reduced AT_1 receptor expression and the authors concluded that mevalonate-GGPP-Rho A pathway played a pivotal role in statin induced changes in AT_1 receptor activity.

Another point is that PPARγ isoform may also participate in AT_1 receptor expression. It has been demonstrated that PPARγ activators: 15-deoxy-PGJ_2, troglitazone and pioglitazone reduced AT_1 receptor expression in cultured VSMCs [115]. Other studies revealed that also HMG reductase inhibitors might influence PPARγ activity. As discussed above, atorvastatin and pravastatin were shown to activate PPARγ [41, 126]. Thus, it is possible that the statin impact on AT_1 receptor expression might be mediated by mevalonate-GGPP-Rho A as well as by PPARγ pathway. However, the above-mentioned hypothesis requires further studies.

The association between AT_1-mediated effects and statins consists not only in their impact on AT_1 expression. It has been shown that statins *via* inhibition of the modification of the small GTP-binding proteins reduced vascular reactive oxygen species (ROS) production induced by angiotensin II. It is known that AT_1 receptor participates in the stimulation of free radical production in VSMCs and it is connected with NAD(P)H oxidase activation. NAD(P)H oxidase is a multicomponent enzyme complex and GTPase Rac1 participates in agonist-mediated activation of this enzyme [120]. Thus, statins, by inhibiting geranylgeranyl-dependent modification of Rac1, might reduce angiotensin II-induced production of superoxide in vascular cells and this is another advantage among beneficial pleiotropic effects of statins.

Interestingly, the linkage between HMGRIs and RAS involves the statin impact on both AT_1 expression and angiotensin converting enzyme activity. Some studies demonstrated that atorvastatin indirectly suppressed ACE up-regulation, *via* reducing vascular endothelial growth factor (VEGF) activity [100]. The very recent studies showed that statins also inhibited ACE induction in differentiating macrophages [101]. The strict mechanism of the described effects is still unknown. However, it is probably connected with a mevalonate pathway and small G proteins; in both cases the suppressive statin activity was reversed by FPP and GGPP.

Benefit-risk assessment of statins in patients with chronic symptomatic heart failure

Hypercholesterolemia-induced AT_1 receptor overexpression may participate in pathophysiology of both atherosclerosis and hypertension with the activation of proliferation and hypertrophy of VSMC. It has been shown in animal studies that AT_1 receptor antagonists inhibited fatty streak formation in arteries in hypercholesterolemia and the observed antiatherogenic effect was not correlated with alterations of lipid levels or blood pressure. The beneficial impact

of ACEI-I and statins on endothelium was already reviewed by Chłopicki et al. [14].

However, pharmacological consequences of interaction between these classes of drugs are not limited only to endothelial function and atherothrombosis, but may involve changes in cardiac performance. Using an animal model of experimental heart failure, Pliquett et al. [87] demonstrated that simvastatin decreased sympathetic outflow with beneficial outcomes in CHF. In that study simvastatin did not significantly affect hemodynamics and left ventricular function. On the other hand, simvastatin-treated rabbits showed lower resting renal sympathetic nerve activity and decreased plasma level of norepinephrine, being a marker of sympathoexcitation. Angiotensin receptor blockade reduces the symphatetic outflow [70], and central angiotensin II contributes to reduced baroreflex sensitivity [69]. Thus, it has been concluded that one of the mechanisms, responsible for the observed changes involved, AT_1 receptor downregulation and altered autonomic tone induced by statins.

The beneficial statin impact on the normalization of sympathetic tone in cardiac insufficiency, demonstrated in animal studies, may suggest the usefulness of HMG-CoA reductase inhibitors in patients with chronic heart failure. Furthermore, some clinical trials indicated an improved survival in ischemic and non-ischemic heart failure in patients receiving statin therapy [43]. Other reports showed the reduction of heart failure incidence in a cohort of patients with coronary heart disease without previous evidence of congestive heart failure [60]. Another positive clinical consequence of the association between statin, AT_1 receptor and CHF is the observation that statins might also ameliorate angiotensin II-induced cardiac hypertrophy and remodeling [21]. As discussed above, angiotensin II, *via* AT_1 receptors, activates proinflammatory NF-κB, important for cardiac hypertrophy and remodeling [98]. The aforementioned molecular pathway of this interference involved a negative statin impact on NF-κB. Summarizing, the above findings indicated a positive role of statins in sympathetic neural control and cardiac hypertrophy, both important for development of cardiac heart failure. Very recently, a randomized, double-blind placebo controlled trial (CORONA) was initiated to answer the question about any benefit-risk in patients with chronic symptomatic heart failure, reduced ejection fraction (NYHA class II–IV) and receiving statin therapy [60].

AT_1 signaling and its implication in possible antihypertensive properties of statins

The coexisting dyslipidemia and hypertension tend to increase the risk of cardiovascular events. As discussed above, hyperlipidemia induced AT_1 receptor overexpression, and patients with high blood pressure (BP) often have an abnormal serum lipid profile [54]. Moreover, there are some evidences linking predisposition for development of both hypertension and dyslipidemia with some genetic risk factors [8].

Some clinical studies showed beneficial effects of statins on BP [7, 30, 37, 73, 88]. Generally, statin treatment was connected with a decrease of 5–8 mmHg in SBP and 3–5 mmHg in DBP. It has not been estimated yet if these reductions in systolic and diastolic were clinically relevant and long-term multicenter studies are needed to evaluate that.

Assessment of BP beneficial statin effect on BP showed, no correlation between a decrease in BP and changes in plasma TG and LDL levels. These findings confirmed the importance of non-lipid-lowering mechanisms in the development of the observed antihypertensive activity of HMG-CoA reductase inhibitors. The suggested mechanism also involved statin impact on renin-angiotensin system. The authors implicated also statin-induced down-regulation of AT_1 receptor expression and receptor density.

Combined therapy, based on a statin and an ACE inhibitor, was shown to display additional BP-lowering effect. For example, the study in hypertensive patients receiving long-term treatment with antihypertensive drugs showed further decrease in systolic BP after pravastatin treatment (from 141.2 ± 4.7 to 136.5 ± 5.3 mmHg), with no significant changes in diastolic BP [49]. In another study, simvastatin monotherapy significantly lowered diastolic BP (–5% compared with –10% with enalapril) [77]. Also combined therapy with simvastatin and enalapril showed greater reduction in diastolic BP compared to subjects receiving an ACE inhibitor alone [111].

Additionally, more improvement of endothelium-dependent vasodilation has been observed during the combined administration of HMGRI and ACEI [63], hence, ACE inhibitors reduce BP by potentiating endothelium-mediated vasodilation. Thus, it has been suggested that the interaction between statin and ACE inhibitor involves both: statin impact on AT_1 expres-

sion as well as its influence on angiotensin II-mediated vascular remodeling.

Another point is that hypertensive subjects were shown to be more responsive to hypolipemic treatment, however, an overall benefit in cardiovascular risk reduction, in primary or secondary prevention, was similar among subjects with or without hypertension [75]. In recent meta-analysis [4] including data of 90056 participants from 14 randomized statin trials, major vascular event reduction per mmol/l of LDL-C decrease was not different between patients with treated hypertension or not. Moreover, the above meta-analysis showed no significant BP reductions resulting from statin treatment [4]. Some explanation of these findings was that antihypertensive drugs might have masked any beneficial effect of statins or that antihypertensive action in hypertensive patients could have been attenuated by a large number of normotensive subjects in whom no effect occurred. In other words, possible heterogeneity of the BP effect of statins (e.g. normal *vs.* hypercholesterolemic or normo- *vs.* hypertensive subjects) in different subjects might account for the discrepancies [75]. Another point is that BP-lowering effect of statins was observed mainly in hypertensive patients.

Interestingly, another proposed mechanism entails statin therapy-induced reduction of synthesis and plasma level of aldosterone [46]. Unfortunately, no other reports pertaining to the link between statin therapy and aldosterone level were found.

Other suggested pathways, not connected with renin-angiotensin system assume also restoration of endothelial dysfunction, increased nitric oxide synthesis or decreased synthesis of ET-1 [75].

Conclusions

HMG-CoA reductase inhibitors are increasingly widely used in greater numbers of patients and their effects extend beyond lipid lowering. These pleiotropic effects include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant effects, anti-inflammatory, immunomodulatory properties and stabilization of atherosclerotic plaques. The inhibition of cardiac hypertrophy is an additional effects of growing interest. Some of the pleiotropic effects of statins are unrelated to the cho-

lesterol-lowering properties of these drugs, but are associated with mevalonate pathway and prenylation process. Recently, the growing interest has been focused on the other mechanisms, like statin impact on the peroxisome proliferator-activated receptor (PPAR), beta-adrenergic signaling or renin-angiotensin system activity, as well as immunomodulatory effects.

These non-lipid-mediated effects and novel pathways discussed in this review may also contribute to statin benefits in cardiovascular events. On the other hand, since a wide spectrum of possible mutual dependences between RAS system or beta-adrenergic and PPAR activity can be expected, thorough studies of statin-other drug interactions and their clinical implications are recommended. Certainly, the pleiotropic effects of statins and other drugs require continued investigation with prospective randomized trials to fully establish their role in the prevention and treatment of cardiovascular events. Moreover, patients will benefit from further research of statin pleiotropy that is focused on establishing targeted therapies and developing new treatment strategies.

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