Atherosclerosis 211 (2010) 9–14

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Effect of HMG-CoA reductase inhibitors on vascular cell apoptosis: Beneficial or detrimental?

Niki Katsiki[a], Konstantinos Tziomalos[a], Yiannis Chatzizisis[b], Moses Elisaf[c], Apostolos I. Hatzitolios[a,*]

[a] 1st Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, 1 Stilponos Kyriakidi Street, 546 36, Thessaloniki, Greece
[b] 1st Cardiology Department, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece
[c] Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

ARTICLE INFO

Article history:
Received 29 September 2009
Received in revised form
30 November 2009
Accepted 18 December 2009
Available online 29 December 2009

Keywords:
Statins
Vascular cell apoptosis
Atherosclerosis
Restenosis

ABSTRACT

Vascular cell apoptosis, an active form of programmed cell death, plays an integral role in atherosclerosis and in-stent restenosis after angioplasty, thus promoting the precipitation of acute cardiovascular events. Beyond their cholesterol-lowering effects, HMG-CoA reductase inhibitors, or statins, have been persistently reported to influence the apoptotic process.

In this review we discuss the effect of statin treatment on vascular cell apoptosis, and therefore on atherosclerosis development, plaque rupture and in-stent restenosis, based on the results of up-to-date experimental and clinical studies. Lipophilic statins have been shown to induce apoptosis in a variety of cell types, including vascular smooth muscle cells and endothelial cells, whereas hydrophilic statins (rosuvastatin and pravastatin) have not. The clinical importance of statin induced apoptosis remains controversial, as it may blunt vascular wall thickening in the early stages of atherosclerosis or reduce the neointimal response to injury on the one hand, but on the other hand it may also promote destabilization of vulnerable plaques precipitating acute cardiovascular events.

Current data support the initiation of statin treatment early enough to inhibit both the formation of atherosclerotic plaques (primary prevention) and in-stent restenosis (secondary prevention).

Contents

1. Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (known as statins) block the conversion of HMG-CoA to mevalonate with consecutive attenuation of the biosynthesis of cholesterol. This effect is associated with a 20–31% and 28–42% reduction in serum total and low-density lipoprotein (LDL) cholesterol, respectively [1,2]. Furthermore, statins exert pleiotropic effects on the vascular wall independent of their cholesterol-lowering properties [3].

Further to the reduction of cholesterol, inhibition of mevalonate by statins leads to a reduction in the synthesis of important intermediate metabolites, such as the isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are involved in the post-translational prenylation of several proteins (i.e. Ras, Rho, Rac) that modulate a variety of cellular processes, including cellular signaling, differentiation, proliferation and apoptosis [4].

During the last decade, several studies have been conducted to investigate the possible impact of these agents on cellular apoptosis on the vessel wall and its potential clinical importance.

* Corresponding author. Tel.: +30 2310 993 480; fax: +30 2310 994 918.
E-mail address: axatzito@med.auth.gr (A.I. Hatzitolios).

0021-9150/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2009.12.028

The aim of this review is to investigate the effect of statins on vascular cell apoptosis, and therefore their role on atherosclerotic plaque formation and plaque rupture, as well as in in-stent restenosis.

2. Methods

MEdline and PubMed databases (up to September 2009) were searched for relevant papers, including original articles and reviews, using combinations of the following keywords: HMG-CoA reductase inhibitor, statin, apoptosis, vascular cell, atherosclerosis, plaque rupture, restenosis.

Moreover, the reference lists of these papers were examined and those judged to be relevant were also selected.

3. Definition of apoptosis and its regulatory pathways

Apoptosis is a form of programmed cell death. Histopathologically, apoptotic cells are characterized by cell membrane shrinkage, active membrane blebbing, nuclear and cytoplasmic condensation, cellular fragmentation and the engulfment of apoptotic bodies by macrophages or neighboring cells, without initiating an inflammatory response [5].

Apoptosis is a highly regulated process, initiated by the absence of survival factors, such as cell–cell and cell–matrix interactions by cadherins, growth factors and shear stress [6], or by death promoting factors such as cytokines, hormones, oxidized LDL (oxLDL), and chemotherapeutic, ionizing or viral agents [7].

There are three major protein families playing a pivotal role in the regulation of cellular apoptosis: caspases, Bcl-2 proteins and IAPs [8,9]. The caspase family consists of more than 14 aspartate-specific cysteinyl proteases, which are expressed as proenzymes in the cytoplasm. On the basis of their functions, caspases are divided into three groups: (1) those with a limited role in apoptosis that participate mainly in inflammation (caspases 1, 4, 5, 11, 12, 13 and 14), (2) those that serve as initiators of apoptosis (caspases 2, 8, 9 and 10) and (3) those that act as effectors of apoptosis (caspases 3, 6 and 7) [10].

The Bcl-2 family consists of more than 15 proteins, which, based upon differences in regulation of apoptosis, are divided into two subgroups: (1) first group, composed of anti-apoptotic proteins (e.g. Bcl-2, Bcl-w and Bcl-X_L) and (2) second group which includes pro-apoptotic proteins and is further subdivided into (i) Bax/bak proteins that allow release of cytochrome *c* and (ii) BH3-only proteins (e.g. Bad, Bid and Bcl-xs) that antagonize the anti-apoptotic Bcl-2 family members [11].

The Inhibitor of Apoptosis Proteins (IAPs) are a conserved family of proteins identified in several species (e.g. virus, fishes, flies, mammals) that antagonize cellular death pathways when overexpressed, mainly by directly binding and inhibiting the pro-apoptotic caspaces 3, 7 and 9 [12]. At physiologic concentrations, mammalian IAPs appear to offer little resistance to apoptosis, partly due to their autoubiquitination and degradation [13]. However, IAPs regulate several other biological activities, including cellular division, morphogenesis and activation of mitogen-activated protein (MAP) kinase and nuclear factor κB (NF-κB) [8]. Consequently, an alternative nomenclature has been proposed for mammalian IAPs, i.e. BIRC [Baculoviral IAP Repeat (BIR)-Containing protein], emphasizing the only structural feature that all IAPs share, i.e. the BIR motif, a sequence of approximately 70 aminoacids that coordinates a zinc ion via histidine and cystine residues [14].

There are two major signaling pathways for the regulation of apoptosis (Fig. 1). The extrinsic pathway concerns membrane-bound death receptors of the tumor necrosis factor-receptor (TNF-R) superfamily, such as Fas/CD95, TNF-R1 and the death receptors DR3, DR4 and DR5 [15]. The binding of the death ligand to its receptor facilitates the activation of procaspase 8 by autoproteolysis and oligomerization, with subsequent proteolytic activation of the effector caspases 3, 6 and 7 [10]. In the intrinsic pathway, various cytotoxic substances may disrupt both the structure and function of the mitochondria by activating pro-apoptotic members of the Bcl-2 family, and may also alter voltage-dependent channels in the mitochondrial membrane leading to cytochrome *c* release into the cytoplasm [16,17]. Once in the cytosol, cytochrome *c* binds to its cytosolic partner, adaptor molecule apoptotic protease activation factor-1 (Apaf-1) and induces the oligomerization of Apaf-1/cytochrome *c* complex in a dATP/ATP-dependent manner [18]. The multimeric complex that is formed is called the apoptosome and recruits and transforms the initiator procaspase 9 into its active form, which in turn triggers the caspase cascade by activating the effector caspases [11].

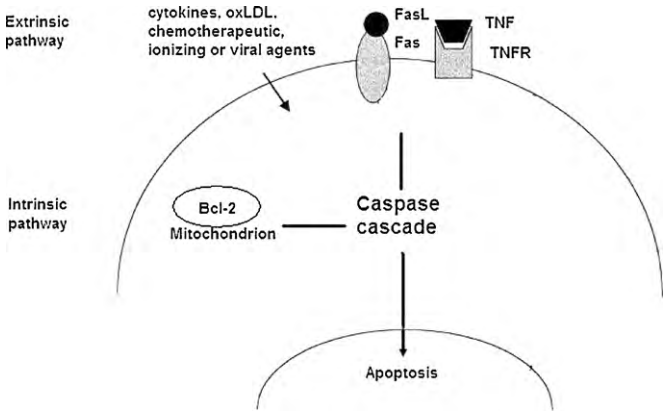

Fig. 1. The two major apoptotic pathways: (a) extrinsic pathway (death receptors such as Fas and TNFR) and (b) intrinsic pathway (Bcl-2 protein family). Both pathways activate the caspase cascade, leading to cell apoptosis (oxLDL: oxidized low-density lipoprotein; FasL: Fas ligand; TNF: tumor necrosis factor; TNFR: TNF receptor).

4. Apoptosis in atherosclerotic plaques

Atherosclerotic lesions typically evolve from an initial 'fatty streak', a region of intimal thickening in response to the presence of inflammatory cells, lipid deposition and lipid-containing macrophages (foam cells) [15]. Progressively, as circulating monocytes continue to infiltrate the lesion, they differentiate into macrophages, express scavenger receptors which engulf ox LDL and transform into foam cells. The accumulation of foam cells forms the lipid core of the plaque. Vascular smooth muscle cells (VSMCs) migrate from the media into the sub-endothelial layer where they acquire a more synthetic phenotype and produce collagen and other extracellular matrix proteins thereby creating the fibrous cap [15]. Adventitial fibroblasts also appear to become activated in response to injury and migrate into the sub-endothelial space where they contribute to the production and deposition of extracellular matrix [19].

Although advanced atherosclerotic lesions can precipitate angina pectoris as a result of gradual narrowing of the vessel lumen, acute cardiovascular events (i.e. unstable angina, myocardial infarction, sudden cardiac death) are generally thought to result from plaque rupture and thrombosis [20]. Rupture-prone (vulnerable) plaques are histologically characterized by a large necrotic lipid core covered by a thin fibrous cap heavily infiltrated by inflammatory cells, a relatively high concentration of foam cells and reduced numbers of VSMCs [21]. Disruption of the fibrous cap usually occurs at the shoulder region of such unstable plaques, where the cap is often thinnest and largely infiltrated with inflam-

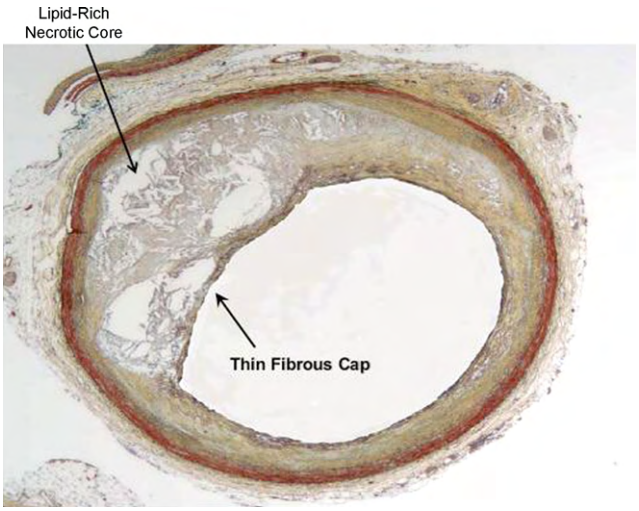

Fig. 2. Thin fibrous cap (vulnerable) atherosclerotic plaque (reproduced with permission from [86]).

matory cells, causing the direct contact of blood coagulation factors to tissue factor and consequently triggering occlusive thrombus formation (Fig. 2) [22].

Apoptosis plays a constant and key role during the evolution of atherosclerosis from atherogenesis to atherosclerotic plaque formation, progression and ultimately rupture [23–25]. Atherosclerotic lesions contain chemically modified lipoproteins, in particular oxLDL, which trigger vascular cells apoptosis [11] via both activation of caspases [26], as well as suppression of the nuclear transcription factor NF-κB [27]. All types of vascular cells undergo apoptosis (i.e. endothelial cells, VSMCs, macrophages and T-lymphocytes) [6,28]. In particular, endothelial cells (EC) in lesion-prone regions, where atherosclerotic plaques preferentially develop, are characterized by increased apoptotic rate, leading to endothelial erosion and dysfunction [29]. Following the initial EC damage, monocytes adhere to the endothelium and transmigrate to the intima, through expression of adhesion molecules, such as intracellular cell-adhesion molecule-1 (ICAM-1) and macrophage chemotactic protein-1 (MCP-1) [15]. The intimal accumulation of inflammatory cells and macrophage-derived foam cells into the arterial wall leads to the formation of the core of the atherosclerotic lesions.

Moreover, VSMCs apoptosis is thought to promote plaque destabilization, as plaques tend to rupture at sites of reduced VSMC contents [30]. Several studies have shown an increased level of VSMC apoptosis in symptomatic plaques in patients presenting with unstable versus stable angina [15,30,31]. VSMC apoptosis leads to a loss of the cells that are mainly responsible for the synthesis of the interstitial collagen fibers, thus resulting in the weakening of the fibrous cup [10,29].

Furthermore, apoptotic VSMC expose on their surface phosphatidylserine, which possesses significant thrombin-generating capacity (possibly by a tissue factor-induced activation of factor X on this anionic phospholipid surface) and therefore increases plaque thrombogenicity [32].

Macrophage apoptosis also promotes plaque destabilization. Loss of macrophages leads to a decrease in scavenging of apoptotic bodies, which can then undergo secondary necrosis, thus contributing to the formation of a necrotic core with high thrombogenicity and immunogenicity [6,29].

Furthermore, vascular cells' apoptosis is associated with the formation of matrix vesicles rich in calcium, suggesting that apoptosis may be important in the calcification of atherosclerotic lesion [33].

Therefore, experimental data strongly support the notion that apoptosis represents a major mechanism responsible for regulation of the cellularity of the arterial wall during atherogenesis [10]. In advanced atheroma, during acute vascular syndromes, massive apoptosis of vascular cells may weaken the fibrous cap, promote thrombosis and increase the risk of plaque disruption [11].

5. Effect of statins on vascular cell apoptosis

During the last decade, several studies have persistently demonstrated that statin treatment can sensitize VSMC to apoptosis or even induce apoptosis in these cells [34–36], although an opposite effect has also been reported [37–39]. Statin induced apoptosis of vascular cells, although still insufficiently understood, may be attributable to the reduced synthesis of important intermediates, such as the isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate, involved in the post-translational prenylation of several proteins (Ras, Rho, Rac) that regulate a variety of cellular processes, including cellular signaling, differentiation and apoptosis [4,40,41]. Protein prenylation is often required for proteins to anchor to the cell membrane and fully function as signal transducers [42]. When their prenylation is inhibited, proteins remain in the cytoplasm and influence various cellular processes. In particular, statin treatment has been shown to inactivate p-21 Rho A protein through inhibition of its prenylation, and subsequently downregulate the expression of anti-apoptotic Bcl-2 protein [36] or stimulate the expression of TNFaR, thereby potentiating TNFa-mediated apoptosis [43]. Moreover, statins have been reported to decrease the expression of survival factors such as survivin [44].

Interestingly, only lipophilic HMG-CoA reductase inhibitors (atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin, pitavastatin) have been shown to enhance VSMC apoptosis, even in the presence of survival factors [45–47]. On the contrary, hydrophilic rosuvastatin and pravastatin have been reported to inhibit the apoptotic process [48,49]. Moreover, apart from VSMC, lipophilic statins are able to stimulate monocyte, macrophage, neutrophil and EC apoptosis [46,50,51].

In particular, atorvastatin has been reported to induce VSMC [36,45] and EC [51] apoptosis in both animal [36,45] and human studies [51].

Simvastatin has also been shown to potentiate EC [43,51] and VSMC apoptosis [34,36,52] in both rats [36,52] and humans [34,51]. Moreover, Chello et al. reported that simvastatin treatment was associated with a significant increase of neutrophil apoptosis in patients undergoing elective coronary bypass grafting surgery, therefore favorably affecting the acute post-operative inflammatory response [53]. On the other hand, in an animal study by Hartung et al. simvastatin supplementation resulted in decreased macrophage apoptosis without influencing VSMC apoptosis [54].

Fluvastatin has been shown to exert pro-apoptotic effects on both human [55] and rat VSMC [56].

Furthermore, Kaneider et al. reported induction of human neutrophil, monocyte and VSMC apoptosis by cerivastatin treatment [46], whereas in a study by Tsujimoto et al. pre-treatment with pitavastatin significantly enhanced apoptosis in human VSMC [47]. It should be noted that cerivastatin was withdrawn from the market in 2001 due to increased incidence of drug-related rhabdomyolysis that led to kidney failure [57].

Interestingly, lovastatin was shown to induce VSMC apoptosis in rats [35,52] although not influencing the apoptotic process in human VSMC in vitro [58] or in cerebral vascular EC culture [59]. In the latter study, lovastatin inhibited TNF-alpha-induced apoptosis of ECs, reflecting its anti-inflammatory effect [59]. Moreover, lovastatin has been reported to protect EC from DNA damage caused by either ionizing radiation [60] or the anticancer drugs doxorubicin and etoposide [61].

Table 1
Effects of statins on vascular cell apoptosis.

Statin	Vascular cell	Apoptosis	Reference
Atorvastatin	VSMC	↑	[36,45]
	EC	↑	[51]
Simvastatin	VSMC	↑ or no effect	[34,36,52,54]
	EC	↑	[43,51]
	Neutrophils	↑	[53]
	Macrophages	↑	[54]
Fluvastatin	VSMC	↑	[55,56]
Cerivastatin	VSMC	↑	[46]
	Monocytes	↑	[46]
	Neutrophils	↑	[46]
Pitavastatin	VSMC	↑	[47]
Lovastatin	VSMC	↑ or no effect	[35,52,58]
	EC	↓ or no effect	[59–61]
Pravastatin	VSMC	↓ or ↑	[34,36,47,49,52,56,66]
	Macrophages	↓	[62]
Rosuvastatin	EC	↓	[64]
	Cardiomyocytes	↓	[48]
	Podocytes	↓	[63]

VSMC: vascular smooth muscle cell; EC: endothelial cell.

Overall, lipophilic statins have been shown to render VSMC and EC more susceptible to apoptosis or even induce apoptosis in these cells; however, a lack of effect has also been reported [37–39].

On the contrary, hydrophilic pravastatin has been reported to suppress VSMC apoptosis in both human [34,47,49] and animal studies [36,52,56] and also to decrease macrophage programmed cell death in human atherosclerotic plaques [62]. Accordingly, hydrophilic rosuvastatin has been shown to attenuate podocyte and cardiomyocyte apoptosis [48,63] in animals and EC apoptosis in humans [64]. A possible explanation for this discrepancy is that hydrophilic statins are highly hepatoselective while the lipophilic ones are much more widely taken up by a broad range of tissues and cells via passive diffusion [34,65]. Only in one study by Weiss RH et al short-term, high-dose, pravastatin incubation was associated with a significant induction of human VSMC apoptosis [66].

The effects of statins on the apoptosis of vascular cells are summarized in Table 1.

Therefore, statin effect on vascular cells apoptosis varies according to type of statin, cell and species, as well as to dosage and duration of drug supplementation. For example, many of the above studies have been performed at high concentrations of drugs, even 100–200-fold above those that are achieved in the plasma [45] and thus relevance to the physiological situation remains unclear [34]. Furthermore, it is not yet known if tissue levels of statins achieved in vivo reach those that have been reported to enhance apoptosis in vitro and if long-term and repeated exposure of vascular cells to whatever tissue levels of those drugs may influence their response to apoptotic signals [34]. Interestingly, acute administration of atorvastatin in animals protect the myocardium against ischemia/reperfusion-associated injury, a beneficial effect that was lost with long-term statin treatment and re-established when an increased dose of atorvastatin was given 3–4 h before ischemia/reperfusion [67]. A potential explanation for this phenomenon was a chronic statin treatment-induced increase in the levels of the tumor suppressor Phosphatase and Tensin homolog deleted on chromosome ten (PTEN), which inactivates phosphatidylinositol-3 kinase (PI3K). Since the activation of PI3K/Atk pathway protects against apoptosis [68], the increase of its main suppressor (i.e. PTEN) may exert a pro-apoptotic effect and attenuate statin-induced cardioprotection. Therefore, it has been suggested that pre-treatment with statin would be beneficial in patients undergoing percutaneous coronary intervention (PCI) even if they are already receiving statins [69,70].

Moreover, the clinical significance of statin effect on vascular cell apoptosis depends on the stage of the disease, i.e. early versus advanced atherosclerotic lesions. Specifically, VSMC apoptosis has been proposed to play a significant role in the control of neointimal thickening [56]. As a logical consequence to the potent pro-apoptotic features of lipophilic statins on VSMC, these agents could potentially play a role in preventing in-stent restenosis. Indeed, animal studies showed an inhibition of neointima formation with lipophilic statins [71,72]. In the clinical setting, however, lipophilic statins did not appear to prevent restenosis in coronary arteries after percutaneous transluminal coronary angioplasty and stenting [73,74]. One explanation for the negative outcome of such clinical trials might be an insufficient drug concentration at the site of neointima formation. If this is the case, stent-based local drug-release at the site of vascular injury via a coated stent would be an appealing method to achieve high local concentrations of drug and avoid systemic toxicity [75]. Thus, statin induced VSMC apoptosis may be beneficial in preventing postangioplasty restenosis or venous graft occlusion [15,35,40,76].

However, an augmented rate of VSMC apoptosis is also found in atherosclerotic lesions, especially in advanced stages, potentially contributing to plaque rupture and increased thrombogenicity and therefore promoting the development of acute coronary events [1,23]. Nevertheless, it should be noted that only lipophilic statins enhance VSMC apoptosis, whereas hydrophilic ones do not, and that their in vitro pro-apoptotic effect is observed at far higher concentrations than those achieved in clinical practice [15]. Furthermore, apart from VSMC content, vulnerability of atherosclerotic plaque is critically dependent on many other factors, including endothelial function, inflammatory status, cytokine production and composition of the extracellular matrix [5]. All types of statins have been reported to exert beneficial antioxidant, antithrombotic and anti-inflammatory effects, thus potentially protecting against different death promoting factors and generally against endothelial dysfunction, atherosclerosis development and progression [1,3,76,77]. Statins are also thought to lessen the propensity for plaque to rupture through a combined reduction in lipids, macrophages and matrix metalloproteinases (proteolytic enzymes secreted by activated macrophages that weaken the fibrous cap of the atherosclerotic plaque) [40,51] and to decrease the vascular expression of adhesion molecules [78]. Therefore, although the clinical importance of statin effect on vascular cell apoptosis remains controversial, these agents through their multiple pleiotropic actions are generally thought to present beneficial effects on the vasculature, protecting against restenosis [76] and atherosclerosis development and also contributing to plaque stabilization [40].

The final clinical outcome of statin effects on vascular cell apoptosis seems to depend on both cell type (i.e. endothelial, neuronal or glial cells) and the current balance between survival and death promoting factors. Further elucidation of this balance may explain the results of clinical trials reporting significant benefits from statin use, but also undesired effects. For example, in a recent large study, SPARCL trial [79], where high doses of atorvastatin were used (80 mg/dl/d), a significant reduction of ischemic strokes was observed [hazard ratio (HR) 0.78; 95% confidence interval (CI) 0.66–0.94] along with an increase in hemorrhagic ones (HR 1.66; 95% CI 1.08–2.55).

Finally, it is of interest that both lipophilic and hydrophilic statins promote the apoptosis of neoplastic cells [80]. In the clinical setting, observational studies suggest that statin use might be associated with reduced risk for any type of cancer and with less aggressive and less advanced breast cancer [81,82]. However, statin

treatment did not affect the risk of cancer in randomized controlled studies [83,84].

6. Conclusions

In summary, apoptosis plays an integral role during atherosclerotic plaque formation, development and rupture. Lipophilic statins, but not hydrophilic, have been widely reported to induce vascular cell apoptosis. The clinical importance of this process remains controversial. On the one hand, increased apoptosis may reduce the neointimal response to injury and therefore prevent vascular wall thickening in early stages of atherosclerosis; while on the other hand, it may promote plaque destabilization and favor the appearance of cardiovascular events in advanced atherosclerotic lesions. However, the regulation of vascular cell apoptosis is complex with multiple interacting molecular pathways and statins also exert beneficial pleiotropic effects on the vasculature. Therefore, the physiological significance of statin induced apoptosis of vascular cells in atherogenesis and plaque instability remains to be determined. Nevertheless, current data support statin treatment both in primary and secondary prevention to inhibit the initial formation of the atherosclerotic plaque, stabilize existing plaques and prevent their rupture, or even prevent restenosis after angioplasty. In addition, despite their different effects on vascular cell apoptosis, both lipophilic and hydrophilic statins are efficient LDL lowering substances that decrease the occurrence of cardiovascular disease (CVD) [85]. Accordingly, current guidelines do not recommend the use of a specific type of statins (i.e. lipophilic or hydrophilic) and suggest that their beneficial role in CVD prevention is largely a class effect [85].

References

[1] Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering-are they clinically relevant? Eur Heart J 2003;24:225–48.
[2] Andrews TC, Ballantyne CM, Hsia JA, Kramer JH. Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins. Am J Med 2001;111:185–91.
[3] McCarey DW, Sattar N, McInnes IB. Do the pleiotropic effects of statins in the vasculature predict a role in inflammatory diseases? Arthritis Res Ther 2005;7:55–61.
[4] Alegret M, Silvestre JS. Pleiotropic effects of statins and related pharmacological experimental approaches. Timely Top Med Cardiovasc Dis 2007;11:E10.
[5] Kavurma MM, Bhindi R, Lowe HC, Chesterman C, Khachigian LM. Vessel wall apoptosis and atherosclerotic plaque instability. J Thromb Haemost 2005;3:465–72.
[6] Mallat Z, Tedgui A. Apoptosis in the vasculature: mechanisms and functional importance. Br J Pharmacol 2000;130:947–62.
[7] Haunstetter A, Izumo S. Apoptosis: basic mechanisms and implications for cardiovascular disease. Circ Res 1998;82:1111–29.
[8] Srinivasula SM, Ashwell JD. IAPs: what's in a name? Mol Cell 2008;30:123–35.
[9] Giam M, Huang DCS, Bouillet P. BH3-only proteins and their roles in programmed cell dearth. Oncogene 2008;27:S128–36.
[10] Geng YJ, Libby P. Progression of atheroma. A struggle between death and procreation. Arterioscler Thromb Vasc Biol 2002;22:1370–80.
[11] Geng YJ. Molecular signal transduction in vascular cell apoptosis. Cell Res 2001;11:253–64.
[12] Dubrez-Daloz L, Dupoux A, Cartier J. IAPs: more than just inhibitors of apoptosis proteins. Cell Cycle 2008;7:1036–46.
[13] Yang YL, Li XM. The IAP family: endogenous caspase inhibitors with multiple biological activities. Cell Res 2000;10:169–77.
[14] Verhagen AM, Coulson EJ, Vaux DL. Inhibitor of apoptosis proteins and their relatives: IAPs and other BIRPs. Genome Biol 2001;2, reviews 3009.1–reviews 3009.10.
[15] Stoneman VE, Bennett MR. Role of apoptosis in atherosclerosis and its therapeutic implications. Clin Sci (Lond) 2004;107:343–54.
[16] Green DR, Reed JC. Mitochondria and apoptosis. Science 1998;281:1309–12.
[17] Scorrano L. Opening the doors to cytochrome *c*: changes in mitochondrial shape and apoptosis. Int J Cell Biol 2009;41:1875–83.
[18] Jiang X, Wang X. Cytochrome *c* promotes caspase-9 activation by inducing nucleotide binding to Apaf-1. J Biol Chem 2000;275:31199–203.
[19] Sartore S, Chiavegato A, Faggin E, et al. Contribution of adventitial fibroblasts to neointima formation and vascular remodeling: from innocent bystander to active participant. Circ Res 2001;89:1111–21.
[20] Shan PK. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol 2003;41(4 Suppl. S):15S–22S.
[21] Glass CK, Witztum JL. Atherosclerosis: the road ahead. Cell 2001;104:503–16.
[22] Libby P, Aikawa M. Stabilization of atherosclerotic plaques: new mechanisms and clinical targets. Nat Med 2002;8:1257–62.
[23] Mallat Z, Tedgui A. Current perspective on the role of apoptosis in atherothrombotic disease. Circ Res 2001;88:998–1003.
[24] Rossi ML, Marziliano N, Merlini PA, et al. Different quantitative apoptotic traits in coronary atherosclerotic plaques from patients with stable angina pectoris and acute coronary syndromes. Circulation 2004;110:1767–73.
[25] Walsh K, Smith RC, Kim HS. Vascular cell apoptosis in remodeling, restenosis and plaque rupture. Circ Res 2000;87:184–8.
[26] Harada-Shiba M, Kinoshita M, Kamido H, Shimokado K. Oxidized low density lipoprotein induces apoptosis in cultured human umbilical vein endothelial cells by common and unique mechanisms. J Biol Chem 1998;273:9681–7.
[27] Heermeier K, Leicht W, Palmetshofer A, Ullrich M, Wanner C, Galle J. Oxidized LDL suppresses NF-kappaB and overcomes protection from apoptosis in activated endothelial cells. J Am Soc Nephrol 2001;12:456–63.
[28] Littlewood TD, Bennett MR. Apoptotic cell death in atherosclerosis. Curr Opin Lipid 2003;14:469–75.
[29] Kockx MM, Herman AG. Apoptosis in atherosclerosis: beneficial or detrimental? Cardiovasc Res 2000;45:736–46.
[30] Bennett MR. Apoptosis of vascular smooth muscle cells in vascular remodelling and atherosclerotic plaque rupture. Cardiovasc Res 1999;41:361–8.
[31] Bauriedel G, Hutter R, Welsch U, Bach R, Sievert H, Lüderitz. Role of smooth muscle cell death in advanced coronary primary lesions: implications for plaque instability. Cardiovasc Res 1999;41:480–8.
[32] Flynn PD, Byrne CD, Baglin TP, Weissberg PL, Bennett MR. Thrombin generation by apoptotic vascular smooth muscle cells. Blood 1997;89:4378–84.
[33] Best PJM, Hasdai D, Sangiorgi G, et al. Apoptosis. Basic concepts and implications in coronary artery disease. Arterioscler Thromb Vasc Biol 1999;19:14–22.
[34] Knapp AC, Huang J, Starling G, Kiener PA. Inhibitors of HMG-CoA reductase sensitize human smooth muscle cells to Fas-ligand and cytokine-induced cell death. Atherosclerosis 2000;152:217–27.
[35] Erl W, Hristov M, Neureuter M, Yan Z-Q, Hansson GK, Weber PC. HMG-CoA reductase inhibitors induce apoptosis in neointima-derived vascular smooth muscle cells. Atherosclerosis 2003;169:251–8.
[36] Blanco-Colio LM, Villa A, Ortego M, et al. 3-Hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors, atorvastatin and simvastatin, induce apoptosis of vascular smooth muscle cells by downregulation of Bcl-2 expression and Rho A prenylation. Atherosclerosis 2002;161:17–26.
[37] Son BK, Kozaki K, Iijima K, et al. Gas6/Axl-PI3K/Akt pathway plays a central role in the effect of statins on inorganic phosphate-induced calcification of vascular smooth muscle cells. Eur J Pharmacol 2007;556:1–8.
[38] Chang WC, Yu YM, Hsu YM, et al. Inhibitory effect of Magnolia officinalis and lovastatin on aortic oxidative stress and apoptosis in hyperlipidemic rabbits. J Cardiovasc Pharmacol 2006;47:463–8.
[39] Atalar E, Ozmen F, Haznedaroglu I, et al. Effects of short-term atorvastatin treatment on global fibrinolytic capacity, and sL-selectin and sFas levels in hyperlipidemic patients with coronary artery disease. Int J Cardiol 2002;84:227–31.
[40] Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Arterioscler Thromb Vasc Biol 2001;21:1712–9.
[41] Vaklavas C, Chatzizisis YS, Ziakas A, Zamboulis C, Giannoglou GD. Molecular basis of statin-associated myopathy. Atherosclerosis 2009;202:18–28.
[42] Casey PJ, Seabra MC. Protein prenyltransferases. J Biol Chem 1996;271:5289–92.
[43] Tang D, Park H-J, Georgescu SP, Sebti SM, Hamilton AD, Galper JB. Simvastatin potentiates tumor necrosis factor α-mediated apoptosis of human vascular endothelial cells via the inhibition of the geranylgeranylation of RhoA. Life Sci 2006;79:1484–92.
[44] Xu YG, Zhou SH, Li YG, et al. The mechanism underlying vascular smooth muscle cell apoptosis induced by atorvastatin may be mainly associated with down-regulation of survivin expression. Cardiovasc Drugs Ther 2007;21:145–53.
[45] Guijarro C, Blanco-Colio LM, Ortego M, et al. 3-Hydroxy-3-methylglutaryl Coenzyme A reductase and isoprenylation inhibitors induce apoptosis of vascular smooth muscle cells in culture. Circ Res 1998;83:490–500.
[46] Kaneider NC, Reinisch CM, Dunzendorfer S, Meierhofer C, Djanani A, Wiedermann CJ. Induction of apoptosis and inhibition of migration of inflammatory and vascular wall cells by cerivastatin. Atherosclerosis 2001;158:23–33.
[47] Tsujimoto A, Takemura G, Mikami A, et al. A therapeutic dose of the lipophilic statin pitavastatin enhances oxidant-induced apoptosis in human vascular smooth muscle cells. J Cardiovasc Pharmacol 2006;48:160–5.
[48] Vilahur G, Casani L, Pena E, Duran X, Juan-Babot O, Badimon L. Induction of RISK by HMG-CoA reductase inhibition affords cardioprotection after myocardial infarction. Atherosclerosis 2009;206:95–101.
[49] Miyashita Y, Ozaki H, Koide N, et al. Oxysterol-induced apoptosis of vascular smooth muscle cells is reduced by HMG-CoA reductase inhibitor. J Atheroscler Thromb 2002;9:65–71.
[50] Liang SL, Liu H, Zhou A. Lovastatin-induced apoptosis in macrophages through the Rac1/Cdc42/JNK pathway. J Immunol 2006;177:651–6.
[51] Dichtl W, Dulak J, Frick M, et al. HMG-CoA reductase inhibitors regulate inflammatory transcription factors in human endothelial and vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 2003;23:58–63.
[52] Sindermann JR, Fan L, Kirsten AW, et al. Differences in the effects of HMG-CoA reductase inhibitors on proliferation and viability of smooth muscle cells in culture. Atherosclerosis 2000;150:331–41.

[53] Chello M, Anselmi A, Spadaccio C, et al. Simvastatin increases neutrophil apoptosis and reduces inflammatory reaction after coronary surgery. Ann Thorac Surg 2007;83:1374–80.
[54] Hartung D, Sarai M, Petrov A, et al. Resolution of apoptosis in atherosclerotic plaque by dietary modification and statin therapy. J Nucl Med 2005;46:2051–6.
[55] Buemi M, Allegra A, Senatore M, et al. Pro-apoptotic effect of fluvastatin on human smooth muscle cells. Eur J Pharmacol 1999;370:201–3.
[56] Takahashi M, Ogata Y, Okazaki H, et al. Fluvastatin enhances apoptosis in cytokine-stimulated vascular smooth muscle cells. J Cardiovasc Pharmacol 2002;39:310–7.
[57] Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Curr Control Trials Cardiovasc Med 2001;2:205–7.
[58] Unlu S, Clunn G, Schachter M, Demoliou-Mason C, Hughes AD. Action of an HMG CoA reductase inhibitor, lovastatin, on apoptosis of untransformed and ts-SV40 transformed human smooth muscle cells derived from saphenous vein. J Cardiovasc Pharmacol 2001;38:161–73.
[59] Lin R, Liu J, Peng N, et al. Lovastatin reduces apoptosis and downregulates the CD40 expression induced by THF-alpha in cerebral vascular endothelial cells. Curr Neurovasc Res 2006;3:41–7.
[60] Nubel T, Damrot J, Roos WP, Kaina B, Fritz G. Lovastatin protects human endothelial cells from killing by ionizing radiation without impairing induction and repair of DNA double-strand breaks. Clin Cancer Res 2006;12:933–9.
[61] Damrot J, Nubel T, Epe B, Roos WP, Kaina B, Fritz G. Lovastatin protects human endothelial cells from the genotoxic and cytotoxic effects of the anticancer drugs doxorubicin and etoposide. Br J Pharmacol 2006;149:988–97.
[62] Crisby M, Nordin-Fredkisson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases and cell death in human carotid plaques: implications for plaque stabilization. Circulation 2001;103:926–33.
[63] Cormack-Aboud FC, Brinkkoetter PT, Pippin JW, Shankland SJ, Durvasula RV. Rosuvastatin protects against podocyte apoptosis in vitro. Nephrol Dial Transplant 2009;24:404–12.
[64] Piconi L, Corgnali M, Da Ros, Assaloni R, Piliego T, Ceriello A. The protective effect of rosuvastatin in human umbilical endothelial cells exposed to constant or intermittent high glucose. J Diabetes Complications 2008;22:38–45.
[65] Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. Trends Pharmacol Sci 1998;19:26–37.
[66] Weiss RH, Ramirez A, Joo A. Short-term pravastatin mediates growth inhibition and apoptosis, independently of Ras, via the signalling proteins p27Kip1 and P13 kinase. J Am Soc Nephrol 1999;10:1880–90.
[67] Mensah K, Mocanu MM, Yellon DM. Failure to protect the myocardium against ischemia/reperfusion injury after chronic atorvastatin treatment is recaptured by acute atorvastatin treatment. J Am Coll Cardiol 2005;45:1287–91.
[68] Brunet A, Bonni A, Zigmond MJ, et al. Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. Cell 1999;96:857–68.
[69] Ellis SG, Anwaruddin S. Recapturing the magic: revisiting the pleiotropic effects of statins in percutaneous coronary revascularization. J Am Coll Cardiol 2009;54:566–8.
[70] Di Sciascio G, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for the Reduction of Myocardial Damage During Angioplasty) randomized trial. J Am Coll Cardiol 2009;54:558–65.
[71] Indolfi C, Cioppa A, Stabile E, et al. Effects of hydroxymethylglutaryl coenzyme A reductase inhibitor simvastatin on smooth muscle cell proliferation in vitro and neointimal formation in vivo after vascular injury. J Am Coll Cardiol 2000;35:214–21.
[72] Chen Z, Fukutomi T, Zago AC, et al. Simvastatin reduces neointimal thickening in low-density lipoprotein receptor-deficient mice after experimental angioplasty without changing plasma lipids. Circulation 2002;106:20–3.
[73] Serruys PW, Foley DP, Jackson G, et al. A randomized placebo controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. Eur Heart J 1999;20:58–69.
[74] Walter DH, Schachinger V, Elsner M, Mach S, Auch-Schwelk W, Zeiher AM. Effect of statin therapy on restenosis after coronary stent implantation. Am J Cardiol 2000;85:962–8.
[75] Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. Circulation 2001;104:600–5.
[76] Erl W. Statin-induced vascular smooth muscle cell apoptosis: a possible role in the prevention of restenosis? Curr Drug Targets Cardiovasc Haematol Disord 2005;5:135–44.
[77] Laufs IU, Liao JK. Direct vascular effects of HMG-CoA reductase inhibitors. Trends Cardiovasc Med 2000;10:143–8.
[78] Kimura M, Kurose I, Russel J, Granger DN. Effects of fluvastatin on leukocyte-endothelial cell adhesion in hypercholesterolemic rats. Arterioscler Thromb Vasc Biol 1998;18:1671–8.
[79] Amarenco P, Goldstein LB, Szarek M, et al. SPARCL Investigators. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 2007;38:3198–204.
[80] Sassano A, Platanias LC. Statins in tumor suppression. Cancer Lett 2008;260:11–9.
[81] Karp I, Behlouli H, Lelorier J, Pilote L. Statins and cancer risk. Am J Med 2008;121:302–9.
[82] Kumar AS, Benz CC, Shim V, Minami CA, Moore DH, Esserman LJ. Estrogen receptor-negative breast cancer is less likely to arise among lipophilic statin users. Cancer Epidemiol Biomarkers Prev 2008;17:1028–33.
[83] Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 2005;366:1267–78.
[84] Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74–80.
[85] Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39.
[86] Insull Jr W. The pathology of atherosclerosis: plaque development and plaque responses to medical treatment. Am J Med 2009;122(1 Suppl.):S3–14.