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Source / Izvornik: **European Journal of Pharmaceutical Sciences, 2022, 178**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1016/j.ejps.2022.106284>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:276332>

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Download date / Datum preuzimanja: **2024-11-07**



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Review

Effect of statins on abdominal aortic aneurysm



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ARTICLE INFO

Keywords:

Abdominal aortic aneurysm

Statins

Inflammation

Oxidative stress

Extracellular matrix

ABSTRACT

Abdominal aortic aneurysm (AAA) is a prevalent condition which causes progressive growth and rupture of aortic wall with a high death rate. Several studies have found that treatment with statins may decrease the progress of AAA and the risk of rupture by suppressing the inflammatory mediators, decreasing oxidative stress, and inhibiting mechanisms involved in extracellular matrix (ECM) degradation. Moreover, some studies have reported that prehospital therapy with statins can decrease mortality after surgery. The novelty of this paper is that different studies including those performed in humans and animals were reviewed and the potential mechanisms by which statins can have an effect on AAA were summarized. Overall, the evidence suggested an association between treatment with statins and improvement of AAA.

1. Introduction

The dilation of abdominal aorta causes abdominal aortic aneurysm (AAA) which is irreversible (Wang et al., 2018). Its prevalence is different in among different populations (Marcaccio and Schermerhorn, 2021). It seems that almost 1.9% to 18.5% males and 0% to 4.2% women suffer from AAA (Ullery and Hallett, 2018). The asymptomatic AAA can cause an undiagnosed AAA, its rupture and surgical emergency (Wang et al., 2018). Aortic rupture often results in sudden death, with the mortality rate above 50% even when the patient undergoes timely surgery (Aoki et al., 2007). Various factors such as hypertension, hypercholesterolemia, family history, male gender, smoking and age may play role in development of AAA (Pande and Beckman, 2008). The most important mechanisms in developing AAA involve inflammation, apoptosis, extracellular matrix (ECM) destruction by proteolytic enzymes, proteolysis and oxidative stress (Chen et al., 2016; Shah, 1997). Surgery is not useful for AAA which is <55 mm in diameter. There are also no well documented pharmacological therapies to reduce the

progression rate and rupture risk of AAA (Ferguson et al., 2010). However, different studies investigated various compounds in animal models of AAA to find effective agents which might reduce the progression or prevent AAA. Small randomized controlled trials have reported that some medication such as roxithromycin (Vammen et al., 2001) and doxycycline (Baxter et al., 2020) could prevent AAA expansion.

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) are the most widely prescribed lipid-lowering medication worldwide. Although several new classes of lipid-modifying agents have been introduced in the past two decades (Kosmas et al., 2021; Sahebkar and Watts, 2013; Sahebkar and Watts, 2013), statins still are the mainstay drugs in the management of atherosclerotic cardiovascular disease. Such an indispensable role not only pertains to the conventional lipid-lowering effects, but also to numerous pleiotropic actions that are seemingly lipid-independent (Dehnavi et al., 2021; Shakour et al., 2020; Sohrevardi et al., 2021; Gorabi et al., 2021; Vahedian-Azimi et al., 2021; Khalifeh et al., 2021; Bland et al., 2022; Bahrami et al., 2018, 2020). In

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<https://doi.org/10.1016/j.ejps.2022.106284>

Received 19 April 2022; Received in revised form 21 July 2022; Accepted 24 August 2022

Available online 26 August 2022

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this context, some observational studies have statins slow down AAA growth. Since matrix metalloproteinases (MMPs) (Thompson and Parks, 1996), especially MMP-9, have the main role in degradation of aortic wall structures (McMillan et al., 1997), the beneficial effect of statins may be related to reduction of MMP activity (Wilson et al., 2005). In this review, we analyze the studies which have evaluated the relationship between AAA and statins.

2. Methods

The articles from different databases such as PubMed, Google Scholar, Science Direct, and Scopus (from 2000 to 2022) were extracted based upon the titles of the articles and the key words. The key words included: “abdominal aortic aneurysm”, “statins”, “matrix metalloproteinases”, “MMP”, “oxidative stress”, “atherosclerosis” and “inflammation”.

The inclusion criteria were: all studies which evaluated the effect of statins on AAA in animal, human, *ex vivo* or *in vitro* studies. The articles were limited to English language. The reference lists of papers identified were also manually searched to find other potentially eligible articles.

2.1. Animal studies

The animal studies were summarized in Table 1. In a study, simvastatin was applied at a dose of 2 mg/kg in elastase-induced-AAA in wild-type or apoE-deficient mice for 14 days. The results showed that simvastatin decreased the development of AAA in both models of normocholesterolemic and apoE-deficient mice. Simvastatin caused a preservation of the structure of arterial wall, it decreased the expression of MMP-9 and increased the level of tissue inhibitor of metalloproteinases-1 (TIMP-1). The prevention of AAA by simvastatin was independent of its lipid-lowering effect (Steinmetz et al., 2005). In another study simvastatin or placebo were administered by gastric lavage in wistar rats with elastase-induced aneurysm before surgery. The infrarenal aorta was separated after 7 days. Simvastatin decreased the aneurysm diameter, it also decreased NF-KB, MMP-9 and oxidative stress. It suppressed some genes including those for interleukin 1, interleukin 4, inducible nitric oxide synthase, P-selectin, platelet-derived growth factor α , tumor necrosis factor, and several chemokines (Kalyanasundaram et al., 2006). In another study, two types of mice were used including those with functional Nrf2 (wild-type (WT) or with transcriptionally inactive form of Nrf2 (transcriptional knockout (tKO)). Angiotensin-II was infused at a dose of 1000ng/kg/day by osmotic mini-pumps for 4 weeks. Simvastatin (20 mg/kg) was administered by intra-gastric gavage 7 days before Ang-II treatment and continued to be administered for 28 days. Ang-II increased the blood pressure and caused vascular damage, inflammation, and oxidative stress which all had a role in development of AAA. Simvastatin decreased the formation of AAA by having effects on Ang-II in both genotypes and it decreased blood pressure in two types of mice. Ang-II increased the expression of VCAM1 (vascular cell adhesion molecule-1) and SELE (E-selectin) expression in tKO mice which was completely inhibited by simvastatin. Ang-II increased the reactive oxygen species in aortic wall while simvastatin did not modify the expression anti-oxidant enzymes (Kopacz et al., 2020). The model of AAA was induced in male *ApoE*^{-/-} mice by osmotic minipumps injecting Ang-II for 28 days. Pravastatin (50mg/kg) was administered by adding to drinking water for 8 weeks. After 28 days, Ang-II caused an enlarging of abdominal aorta diameter. Moreover, pravastatin increased the incidence of AAA, mortality and severity of AAA in Ang-II group. However, pravastatin promoted AAA in *ApoE*^{-/-} mice. Pravastatin also increased MMP2, AMP-activated kinase alpha 2 (AMPK α 2) and alpha protein 2 (AP-2 α) in cultured vascular smooth muscle cells (VSMCs). The results of this study indicated that pravastatin promoted AAA formation through AMPK α 2-dependent AP-2 α activations and an increase of Ang-II-induced AAA occurred (Ma et al., 2017). In another study, the anti-AAA effect of atorvastatin against

elastase-induced AAA in rats was evaluated. Atorvastatin caused a decrease of aneurysm diameter when compared with control group. It suppressed migration of macrophages to aortic wall one week after surgery, it prevented the expression of ICAM and MCP-1 which caused an inhibition of MMP12. It also increased the synthesis of collagen and elastin in the aortic wall. However, attenuation of AAA development by atorvastatin may be related to anti-inflammatory effect of this drug (Shiraya et al., 2009). In another study apoE^{-/-} male mice received rosuvastatin (10mg/kg/day) and atorvastatin (20mg/kg/day) by drinking water for 1 week before starting to receive an Ang-II infusion. Ang-II caused AAA and a dilation of aorta diameter after 28 days. The findings of this research suggested that statins had no significant effects against AAA induced by Ang-II. However, their effects on atherosclerosis were different. Atorvastatin decreased atherosclerotic lesion areas and accumulation of lymphocytes. Atorvastatin also upregulated anti-inflammatory genes without any effect on inflammatory cytokines and serum lipids concentrations (Wang et al., 2011). When atorvastatin was applied in two models of aneurysm, including AAA induced by Ang II in ApoE^{-/-} mice and CaCl₂-induced AAA in C57 mice, atorvastatin was able to suppress the development of AAA in both models. Endoplasmic reticulum (ER) signaling pathway and inflammatory responses have a role in formation of AAA following Ang-II infusion. Atorvastatin caused a decrease of occurrence of AAA, which may be related to attenuation of ER stress signaling proteins, apoptotic cells, and the promotion of Caspase12 and Bax. It also reduced cytokines that play an important role in inflammation such as IL-6, IL-8 and IL-1 β . In an *in vitro* study vascular smooth muscle cells and RAW264.7 were exposed to simvastatin and then after 1 h Ang-II was added for 24 h. Simvastatin inhibited apoptosis pathway and ER signaling in both cell lines (Li et al., 2017). In a study in which AAA was created by infusion of porcine pancreatic elastase and application of plastic cuff the atorvastatin group (1mg/kg/day) was compared with control group after 28 days. There was no difference between statin group and the group which was not treated with a statin. Atorvastatin has beneficial effects on post-operative histological feature of aortic elastin network, on protection of contractile fibers of vascular smooth muscle cell, a higher vasa vasorum density, as well as on prevention of intima and media thickening. Therefore, atorvastatin may inhibit the occurrence and reduce the further development of AAA (Houdek et al., 2013). A study showed that intravenous administration of nanoparticles of pitavastatin (containing 0.12mg/kg/week) in Ang-II-induced AAA in ApoE^{-/-} mice decreased AAA development, which was related to reduction of macrophage accumulation and MCP-1 expression. It decreased the activity of MMPs and elastin degradation (Katsuki et al., 2021) (Table 1).

2.2. Human studies

The *ex vivo* and clinical studies are shown in Table 2. In a study, the specimens of aortic aneurysm wall were isolated from 10 patients with AAA and aortic specimens were obtained from nine patients with aortoiliac occlusive disease as control for evaluation by immunohistochemical analysis. In one group the specimens were exposed to various concentrations of cerivastatin (0.001 to 0.1 mol/L) for 48 h. Cerivastatin reduced total and active MMP-9 in a dose dependent way by prevention of the activation of macrophages and neutrophils (Nagashima et al., 2002). The patients with large AAA were divided into two groups, one group received simvastatin at a dose of 40mg/kg/day for 3 weeks before surgery while the other group took placebo. During surgery, a section of aneurysm wall was separated and the level of MMP-9 was evaluated in both groups. The findings showed that statin therapy suppressed MMP-9 production suggesting that that statin therapy could be useful for the prevention or treatment of AAA (Evans et al., 2007). In another study, 63 patients without symptoms of AAA had selective surgery. 17 of them were treated with a statin before the surgery and the other with placebo. The sections of the aortic wall were isolated during the surgery and different types of MMP were evaluated. The results showed that statin

Table 1
Effect of statins on AAA in animal studies.

Type	Study design	drugs	Duration of study	dose	result	Ref.
<i>In vivo</i>	Animal study (rat)	Elastase-induced-AAA in normo cholesterolemic and apoE-deficient rats	Simvastatin	14 days	2mg/kg	Preservation of structure wall MMP-9 TIMP-1 (Steinmetz et al., 2005)
<i>In vivo</i>	Animal Study (rat)	Administration of statin by gastric lavage in elastase-induced-aneurysm before surgery	Simvastatin	Separation of aorta after 7 days	60mg/kg/day	Aneurysm diameter, NF- κ B, MMP-9, oxidative stress, interleukin 1, interleukin 4 (Kalyanasundaram et al., 2006)
<i>In vivo</i>	Animal Study (mice)	Infusion of Ang-II for 4 weeks	Simvastatin	Administration of simvastatin by intragastric lavage for 5 weeks	20mg/kg	Blood pressure, VCAM and SELE (Kopacz et al., 2020)
<i>In vivo</i>	Animal study (mice)	Infusion of Ang-II in Apo-E mice for 4 weeks	Pravastatin	Pravastatin was given via drinking water for 8 weeks	50mg/kg	incidence of AAA, mortality and severity of AAA (Ma et al., 2017)
<i>In vitro</i>	Cell culture	Ang-II-induced AAA in VSMCs for 24h	Pravastatin	The cells were exposed to pravastatin for 30 min	50 μ M	MMP2 AMPK α 2 AP-2 α (Ma et al., 2017)
<i>In vivo</i>	Animal study (rat)	Infusion of elastase-induced AAA for 30min	Atorvastatin	Drug was given daily until harvest.	20mg/kg/day	MMP-12, MMP-2, MMP-3, MMP-9, MCP-1 and ICAM (Shiraya et al., 2009)
<i>In vivo</i>	Animal Study (mice)	Infusion of Ang-II-induced AAA in apo-e mice for 4 weeks	Rosuvastatin or Atorvastatin	Administration of drugs by drinking water for 5 weeks	Rosuvastatin (10 mg/kg/day) and atorvastatin (20mg/kg/day)	These statins had not significant effects against AAA (Wang et al., 2011)
<i>In vivo</i>	Animal study (mice)	AAA induced by Ang II in ApoE ^{-/-} mice for 28 days	Atorvastatin	Administered by lavage for 5 weeks	20 or 30 mg/kg/day	Reduced ER stress signaling proteins, the number of apoptotic cells, and the activation of Caspase12 and Bax (Li et al., 2017)
<i>In vitro</i>	Vascular smooth muscle cells (VSM CS) and Raw 264.7 cells	CaCl ₂ -induced AAA in C57 mice The cells were exposed to Ang-II for 24h	Simvastatin	Administered by lavage for 7 weeks Added before to Ang-II exposure	20mg/kg/day 0.1, 1 and 10 μ mol/l	Inhibition of ER stress signaling pathway and apoptosis dose dependently in both types of cells (Li et al., 2017)
<i>In vivo</i>	Animal study	AAA was induced by infusion of porcine pancreatic elastase	Atorvastatin	28days	1mg/kg/day	Atorvastatin has no effect on diameter of aorta but has preventive effects on histopathological AAA (Houdek et al., 2013)
<i>In vivo</i>	Animal study (mice)	Ang-II-induced AAA in ApoE ^{-/-} mice	Pitavastatin	Administered by tail vein for 4 weeks	Administration of nanoparticles containing 0.12mg/kg/week intravenously	MMPs MCP-1 Macrophage accumulation (Katsuki et al., 2021)

Abbreviations: Abdominal aortic aneurysm (AAA), Monocyte chemoattractant protein-1 (MCP-1), nuclear factor kappa B (NF- κ B), matrix metalloproteinases (MMP), tissue inhibitors of metalloproteinases (TIMP), E-selectin (SELE), vascular cell adhesion molecule-1 (VCAM1), AMP-activated kinase (AMPK), alpha protein 2 (AP-2 α), intercellular adhesion molecule 1 (ICAM), endoplasmic reticulum (ER).

treatment decreased the level of MMP-9 and MMP-3 when compared with placebo (Wilson et al., 2005). In a retrospective study 211 patients were divided into two groups – one treated with a statin and the other group did not receive a statin. The patients were followed up for one year. The study showed that the growth rate of diameter decreased in statin group when compared with non-statin group (Karrowini et al., 2011). Extensive aortic atheroma is common in AAA patients and it usually has an irregular appearance. In a retrospective study, statins were administered to AAA patients. The comparison before and after statin administration showed that statins reduced the extensive aortic atheroma which was an effect that could be related to the pleiotropic effects of statins (Nemoto et al., 2013). A cohort study showed that AAA patients who had open surgery and received statins had beneficial effects concerning long-term survival and early mortality (Mathisen and Abdelnoor, 2017). A clinical trial showed that treatment with statins during the preoperative period caused better survival when compared with patients who did not take statins (O'Donnell et al., 2018). The specimens of aorta wall were obtained from patients during surgery and exposed to different concentrations of simvastatin. The results showed that simvastatin prevented NF- κ B activation. Simvastatin also decreased the secretion of MMP-9, monocyte chemoattractant protein (MCP)-2 and epithelial neutrophil-activating peptide (CXCL5). However, anti-AAA effect of statins can be related to inhibition of Rac1/NF- κ B pathway

which causes suppression of MMP-9 and chemokine secretion in human AAA (Yoshimura et al., 2015). A meta-analysis of 11 observational studies based on 4647 AAA patients indicated that statin therapy prevents the growth of small AAAs (<55 mm in diameter) (Takagi et al., 2012). Another meta-analysis on 11933 AAA patients showed that statin therapy seemed to improve all-cause survival after AAA repair (Twine and Williams, 2011). In a study in which simvastatin or atorvastatin were administered to AAA patients that used statins for at least 6 weeks and who had an open AAA repair. Both statins caused a decrease of NF- κ B, inflammatory mediators such as IL-6 and MCP-1, cysteine protease, as well as macrophage-related markers e.g. cathepsin K and S. However, despite anti-inflammatory effects of statins, these drugs did not reduce AAA growth rate (van der Meij et al., 2013) (Table 2). Different studies have demonstrated that administration of statins in AAA patients can have positive effects and could reduce progression of AAA, rupture and perioperative mortality.

2.3. Potential mechanisms of action

AAA is a severe disease which can cause rupture and death if not treated. The important pathological process of AAA pathogenesis involves an increase of inflammation factors such as monocyte chemoattractant protein-1 (MCP-1) and infiltration of macrophages, activation

Table 2
Effect of statins on AAA in clinical and *ex vivo* studies.

Type	Study design	drugs	Duration of study	dose	result	Ref.
<i>Ex vivo</i> study	The aortic specimen was isolated from 10 patients with infrarenal AAA	Cerivastatin	48h	0.001-0.1 mol/l	MMPs Activation of macrophages and neutrophiles	(Nagashima et al., 2002)
<i>Ex vivo</i> study	During the surgery, a section of aneurysm wall was separated in patients with large AAA	Simvastatin	3 weeks before surgery	40mg/kg	MMP-9 in comparison with control group	(Evans et al., 2007)
Human study	211 patients were divided into two groups. 136 patients in the statin and 75 patients in the non-statin group. AAA diameter in two groups was measured by serial imaging surveillance. for one year	Statin users were identified as patients who were on any statin therapy at the initial imaging study. Non-statin users were identified as patients not on any statin during the entire study period.	One year	Not mentioned	The growth rate of diameter in statin group was lower than non- statin group	(Karrowni et al., 2011)
Human study	Contrast-enhanced computed tomography (CECT) was used to examine thoracic aortas of 29 patients (statin group; n = 22, non-statin group; n = 7) with extensive atheromas	Pitavastatin (n = 7), atorvastatin (n = 7), rosuvastatin (n = 4), fluvastatin (n = 2), simvastatin (n = 1), and pravastatin (n = 1)	897 days	Not mentioned	This pilot study showed that the area of atheroma decreased after administration of statins, and the atheroma reduction ratio was significant (P < 0.01).	(Nemoto et al., 2013)
Human study	A retrospective cohort study was performed to compare early and total mortality for all patients treated for AAA with open surgery who were taking statins compared to those who were not.	Statin therapy	The median follow-up was 3.93 years,	Not mentioned	This retrospective cohort study showed a significantly beneficial effect of statin use on early and long-term survival for AAA patients treated with open surgery.	(Mathisen and Abdelnoor, 2017)
Human study	37950 patients with AAA repair (29,257 endovascular and 8693 open) entered this study	Statin therapy	2.9 years	Not mentioned	Preoperative statin use was associated with higher adjusted 1-year (94% vs 90%) and 5-year (85% vs 81%) survival (P < .001) compared with those who were not taking a statin, whereas those who started a statin therapy postoperatively also had higher 1-year (94% vs 91%) and 5-year (89% vs 81%) survival (P < .001).	(O'Donnell et al., 2018)
<i>Ex vivo</i> study	The specimens of aorta wall were obtained from patients during surgery and exposed to different concentrations of simvastatin	Simvastatin	between 48 and 96 h	10 µM	NF-KB activation MMP-9 MCP-2	(Yoshimura et al., 2015)
Human study	Twelve cohort studies including 11933 AAA patients were reviewed	Statin therapy	-	Any dose of statin therapy	Statin therapy seemed to improve all-cause survival after AAA repair	(Twine and Williams, 2011)
<i>Ex vivo</i> study	An observational study was done in patients who were not treated with a statin (control group, n = 25), who were treated with an intermediate dose (20 mg/day simvastatin or atorvastatin, n = 28) and high dose statin (40 mg/day simvastatin or atorvastatin, n = 10). Statins were administered for at least 6 weeks and patients underwent an open AAA repair. Then aortic wall tissue was taken from the anterior-lateral aneurysm	Simvastatin or atorvastatin	At least 6 weeks	20 or 40 mg/day	Inflammatory Mediators: IL-6 and MCP-1, cysteine protease, macrophage-related markers e.g. cathepsin K and S did not reduce AAA growth	(van der Meij et al., 2013)

Abbreviations: Abdominal aortic aneurysm (AAA), Monocyte chemoattractant protein-1 (MCP-1), nuclear factor kappa B (NF-κB), Matrix metalloproteinases (MMP)

of matrix metalloproteinase (MMP), the vascular media is degenerated and elastic fibers are damaged (Daugherty et al., 2011). The mechanism by which statins might control AAA is unclear but there are some studies indicating probable mechanisms (Fig. 1).

2.4. Nrf2 pathway

In physiological condition Nrf2 exists in a complex with Keap-1 and in stress Nrf2 is released and causes antioxidant response element- (ARE-) mediated genes expression (Loboda et al., 2016). Nrf2 stimulates anti-oxidant genes and may have protective effect on VSMC. It also reduces pro-inflammatory mediators (Choi et al., 2015). The studies have reported that the deficiency of Nrf2 increased the expression of inflammatory mediators such as MCP1, IL6, and TNFα (Ruotsalainen et al.,

2013) and contributed to AAA formation and rupture (Song et al., 2020). Therefore, increasing of Nrf2 expression can have role in prevention of AAA. The activity of Nrf2 is reduced in an age-dependent way and it can have a role in development of diseases such as AAA (Kloska et al., 2019). Activation of Nrf2 can have beneficial effect on AAA (Kloska et al., 2019). The studies have reported protective effect of rosuvastatin in atrial fibrillation by activation of Akt/Nrf2/HO-1 pathway (Yeh et al., 2015). Atorvastatin reduced Ang-II induced oxidative stress by regulation of Nrf2 which might additionally explain the role of Nrf2 in AAA (Fig. 2) (Ma et al., 2014).

2.5. HO-1 pathway

Hem-oxygenase (HO-1) as a cytoprotective enzyme has different

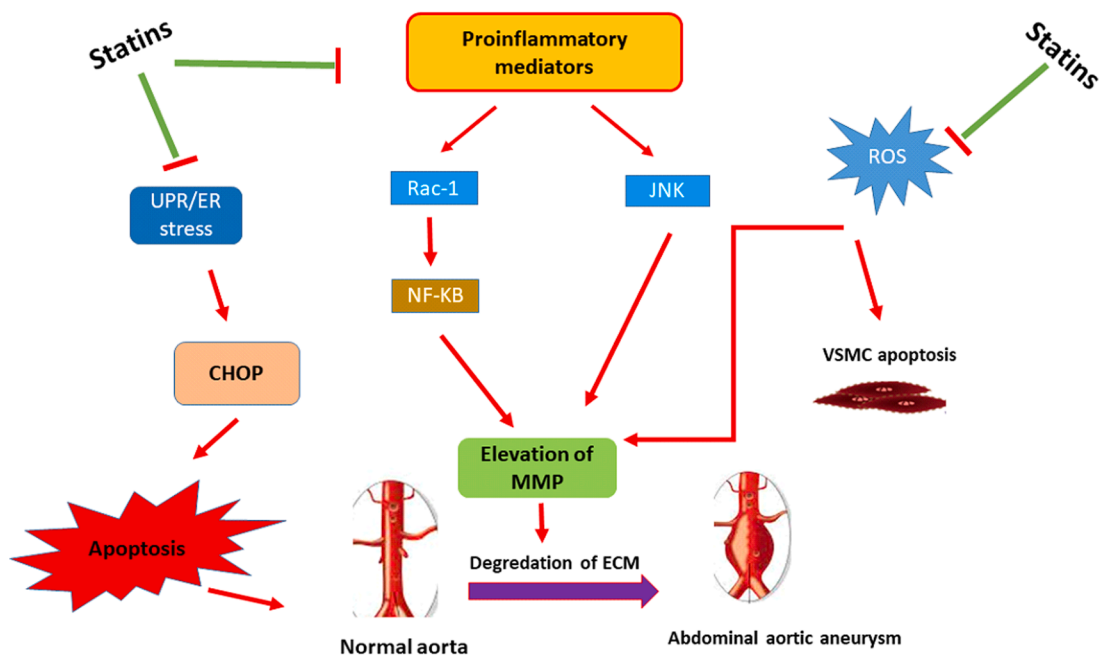


Fig. 1. Effect of statins on various pathway signaling to reduce development of AAA. Vascular smooth muscle cell (VSMC), Jun N-terminal kinases (JNK), (Rac-1), Nuclear factor-KB (NF-KB), Extracellular matrix (ECM), Unfolded protein response (UPR), Endoplasmic reticulum (ER), C/EBP homologous protein (CHOP), Reactive oxygen species (ROS).

properties such as immunomodulatory, anti-inflammatory, anti-apoptotic, anti-proliferative, anti-oxidant, and effects on vascular cells (Araujo et al., 2012). The studies have reported that the decrease of HO-1 expression might have a role in development of AAA (Azuma et al., 2016). In porcine pancreatic elastase (PPE)-induced AAA model in HO-1 heterozygous mice, deficiency of HO-1 caused development of AAA and an increase of pro-inflammatory cytokines in macrophages such as

MCP-1, TNF- α , IL-6 and IL-1- β while the level of anti-inflammatory factors including TGF- β and IL-10 decreased (Azuma et al., 2016). Rosuvastatin in low doses suppressed AAA progression in an AAA model by inducing HO-1 expression in aortic tissue even in the absence of lipid lowering. (Azuma et al., 2016). Some other studies have reported that treatment with statins increases the expression of HO-1 in heart and lung tissues (Hsu et al., 2006; Lee et al., 2004). The increase of HO-1 causes a

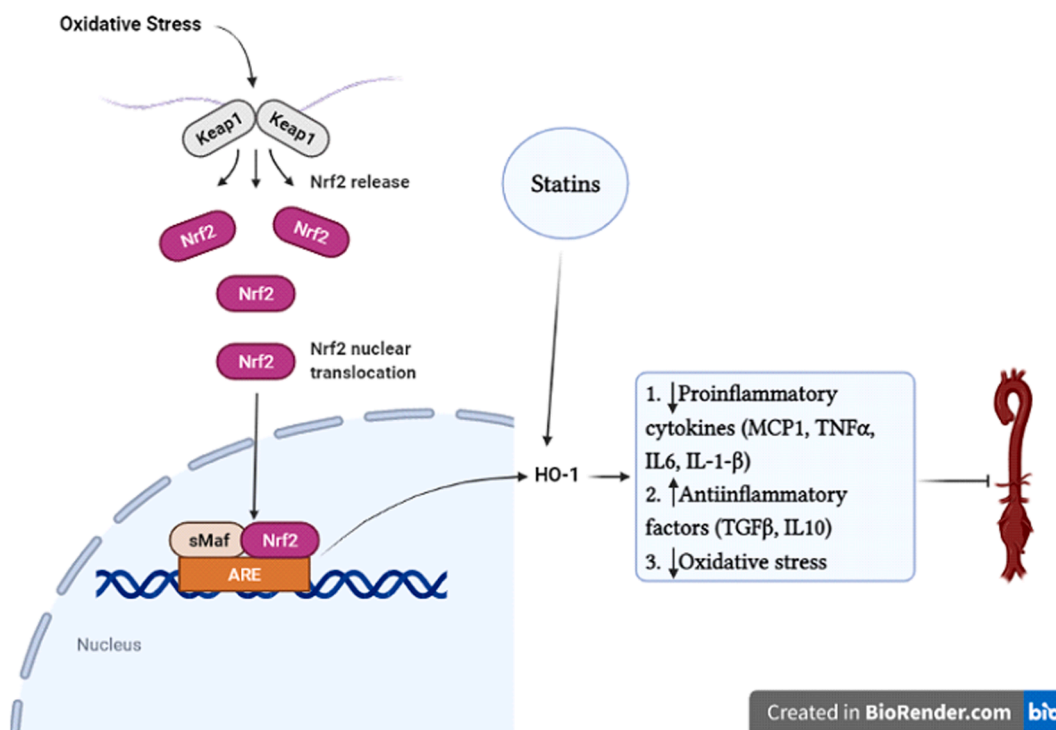


Fig. 2. Effects of statins on Nrf2/HO-1 signaling pathway to reduce AAA development. Nuclear factor erythroid 2-related factor 2 (Nrf2), Heme oxygenase-1 (HO-1), Kelch-like ECH-associated protein 1 (keap1), antioxidant response element (ARE), small musculoaponeurotic fibrosarcoma proteins (sMAF), monocyte chemo-attractant protein-1 (MCP-1).

decrease of inflammation and oxidative stress which are important factors in development of AAA.

2.6. Inhibition of MMP

In vivo and *in vitro* studies have indicated that overexpression of MMPs 1, 3, 8, 9 and 13 might have a role in progression and rupture of AAA (Sakalihasan et al., 1996; Crowther et al., 2000). The studies have reported that statins inhibit MMP expression in atherosclerotic lesions (Molloy et al., 2004) and AAA (Wilson et al., 2005; Nagashima et al., 2002). Simvastatin reduced MMP-9 and TIMP-1 (Steinmetz et al., 2005; Kalyanasundaram et al., 2006), atorvastatin had effects on prevention of MMP-12 via inhibition of ICAM-1 and MCP-1 expression (Shiraya et al., 2009), and cerivastatin decreased the level of MMP-9 in human organ culture system (Nagashima et al., 2002).

2.7. Anti-oxidant effects

Reactive oxygen species (ROS) and overexpression of pro-oxidant enzymes have an important role in development of human aortal aneurysm (Miller et al., 2002). ROS have an effect on c-Jun N-terminal kinase (JNK) and nuclear factor kappa B (NF- κ B) (Diehm et al., 2007). Simvastatin prevents free radicals formation, TNF α production and elevation of anti-oxidant capacity by inhibition of NF- κ B (Piechota-Polanczyk et al., 2012). The expression of inducible nitric oxide synthase (iNOS) has a role in formation of aneurysm in animal models (Lee et al., 2001; Johanning et al., 2002) and humans (Zhang et al., 2003). Simvastatin has role in prevention of AAA by downregulation of iNOS expression (Kalyanasundaram et al., 2006). Therefore, one of the anti-AAA mechanisms can be inhibition of iNOS (Johanning et al., 2002).

2.8. Synthesis of ECM

The extracellular matrix (ECM), with collagen type I and elastin are important components of the aortic wall. The degradation of ECM proteins, especially elastin and collagen, can initiate AAA (Adams et al., 2021). The studies have shown that pro-inflammatory factors activate enzymes, which have an important role in degradation of ECM such as MMP 2 and 9 while they decrease lysyl oxidase (LOX) which increases the expression of ECM synthesis (Hellenthal et al., 2009). Statins may have effects on ECM remodeling by inhibition of MMPs.

2.9. Decreasing of TNF- α

The level of TNF- α is increased in patients with AAA and inhibition of TNF- α has an important role in preventing aneurysm formation (Xiong et al., 2009). Simvastatin decreased TNF- α , IL-6 and IL-1b in patients with hypercholesterolemia (Krysiak et al., 2011). It also reduced inflammatory factors in rat model of cardiopulmonary bypass (Shen et al., 2010). Simvastatin attenuated different interleukins (IL-4,5, 6,8 and 10), TNF- β and INF- γ in AAA. It also prevented the recruitment of T lymphocytes and macrophages in aortic wall (Hurks et al., 2010).

2.10. Regulation of endoplasmic reticulum (ER) stress

Endoplasmic reticulum (ER) stress signaling can cause a dysfunction of tissues and cells (Wang and Kaufman, 2012). Studies have shown that ER stress has an important role in development of heart failure, atherosclerosis and other cardiovascular diseases by activation of C/EBP homologous protein (CHOP) - which causes inflammation and apoptosis

(Hotamisligil, 2010, 2010). Recent studies have shown that ER stress might be one of the mechanisms which play a role in AAA progression (Li et al., 2017). Yuanyuan et al. have reported that the suppression of AAA development by statins may be related to attenuation of ER stress signaling and ER stress-associated apoptosis as well as inflammatory response (Li et al., 2017). Simvastatin prevents the ER stress associated apoptosis signaling pathways in VSMC and RAW264.7. Atorvastatin reduces Ang-II-induced AAA in mice by suppression of ER stress pathway (Li et al., 2017). Statins suppressed the inflammation and apoptosis in the aorta by down-regulation of the PERK-p-EIF2 α -CHOP associated ER stress signaling pathway (Li et al., 2017).

3. Conclusion

Several studies on animal models as well as on patients have reported that a relationship exists between treatment with statins and progression of AAA. Most statins decrease or prevent AAA by different mechanisms such as regulation of ER, anti-oxidantion, synthesis of ECM, inhibition of MMPs, attenuation of TNF- α , NF- κ B and other mechanisms. Because of beneficial effects of statins in cardiovascular disease, their low cost and relative safety of statins, they may be appropriate candidates to be prescribed by physicians in AAA patients. Of course, different effects of statins on AAA may be related to different types of statins, doses, duration of treatment and different AAA models.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

- Wang, Y.-D., Liu, Z.-J., Ren, J., Xiang, M.-X., 2018. Pharmacological therapy of abdominal aortic aneurysm: an update. *Curr. Vasc. Pharmacol.* 16 (2), 114–124.
- Marcaccio, C.L., Schermerhorn, M.L., 2021. Epidemiology of abdominal aortic aneurysms. *Seminars in Vascular Surgery*. Elsevier.
- Ullery, B.W., Hallett, R.L., 2018. Fleischmann D. Epidemiology and contemporary management of abdominal aortic aneurysms. *Abdom. Radiol.* 43 (5), 1032–1043.
- Aoki, H., Yoshimura, K., Matsuzaki, M., 2007. Turning back the clock: regression of abdominal aortic aneurysms via pharmacotherapy. *J. Mol. Med.* 85 (10), 1077–1088.
- Pande, R.L., Beckman, J.A., 2008. Abdominal aortic aneurysm: populations at risk and how to screen. *J. Vasc. Interv. Radiol.* 19 (6), S2–S8.
- Bland, AR, Payne, FM, Ashton, JC, Jamialahmadi, T, Sahebkar, A, 2022 Jan. The cardioprotective actions of statins in targeting mitochondrial dysfunction associated with myocardial ischaemia-reperfusion injury. *Pharmacol. Res.* 175, 105986. <https://doi.org/10.1016/j.phrs.2021.105986>.
- Chen, H.-Z., Wang, F., Gao, P., Pei, J.-F., Liu, Y., Xu, T.-T., et al., 2016. Age-associated sirtuin 1 reduction in vascular smooth muscle links vascular senescence and inflammation to abdominal aortic aneurysm. *Circ. Res.* 119 (10), 1076–1088.
- Shah, P.K., 1997. Inflammation, metalloproteinases, and increased proteolysis: an emerging pathophysiological paradigm in aortic aneurysm. *Circulation* 96 (7), 2115–2117.
- Ferguson, C.D., Clancy, P., Bourke, B., Walker, P.J., Dear, A., Buckenham, T., et al., 2010. Association of statin prescription with small abdominal aortic aneurysm progression. *Am. Heart J.* 159 (2), 307–313.
- Vammen, S., Lindholt, J.S., Østergaard, L., Fasting, H., Henneberg, E., 2001. Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. *Br. J. Surg.* 88 (8), 1066–1072.
- Baxter, B.T., Matsumura, J., Curci, J.A., McBride, R., Larson, L., Blackwelder, W., et al., 2020. Effect of doxycycline on aneurysm growth among patients with small infrarenal abdominal aortic aneurysms: a randomized clinical trial. *JAMA* 323 (20), 2029–2038.
- Kosmas, C.E., Pantou, D., Sourlas, A., Papakonstantinou, E.J., Echavarría Uceta, R., Guzman, E., 2021. New and emerging lipid-modifying drugs to lower LDL cholesterol. *Drugs Context* 10.

- Sahebkar, A., Watts, G.F., 2013. New therapies targeting apoB metabolism for high-risk patients with inherited dyslipidaemias: what can the clinician expect? *Cardiovasc. Drugs Ther.* 27 (6), 559–567.
- Sahebkar, A., Watts, G.F., 2013. New LDL-cholesterol lowering therapies: pharmacology, clinical trials, and relevance to acute coronary syndromes. *Clin. Ther.* 35 (8), 1082–1098.
- Dehnavi, S., Kiani, A., Sadeghi, M., Biregani, A.F., Banach, M., Atkin, S.L., et al., 2021. Targeting AMPK by statins: a potential therapeutic approach. *Drugs* 81 (8), 923–933.
- Shakour, N., Ruscica, M., Hadizadeh, F., Cirtori, C., Banach, M., Jamialahmadi, T., et al., 2020. Statins and C-reactive protein: in silico evidence on direct interaction. *Arch. Med. Sci.* 16 (6), 1432–1439.
- Sohrevardi, S.M., Nasab, F.S., Mirjalili, M.R., Bagherniya, M., Tafti, A.D., Jarrahzadeh, M.H., et al., 2021. Effect of atorvastatin on delirium status of patients in the intensive care unit: a randomized controlled trial. *Archives of medical science*, 17. AMS, p. 1423.
- Gorabi, A.M., Kiaie, N., Bianconi, V., Pirro, M., Jamialahmadi, T., Sahebkar, A., 2021. Statins attenuate fibrotic manifestations of cardiac tissue damage. *Curr. Mol. Pharmacol.* 14 (5), 782–797.
- Vahedian-Azimi, A., Mohammadi, S.M., Beni, F.H., Banach, M., Guest, P.C., Jamialahmadi, T., et al., 2021. Improved COVID-19 ICU admission and mortality outcomes following treatment with statins: a systematic review and meta-analysis. *Archives of Medical Science*, 17. AMS, p. 579.
- Khalifeh, M., Penson, P.E., Banach, M., Sahebkar, A., 2021. Statins as anti-pyrototic agents. *Archives of Medical Science*, 17. AMS, p. 1414.
- Thompson, R.W., Parks, W.C., 1996. Role of matrix metalloproteinases in abdominal aortic aneurysms. *Ann. N.Y. Acad. Sci.* 800 (1), 157–174.
- McMillan, W.D., Tamarina, N.A., Cipollone, M., Johnson, D.A., Parker, M.A., Pearce, W.H., 1997. Size matters: the relationship between MMP-9 expression and aortic diameter. *Circulation* 96 (7), 2228–2232.
- Wilson, W., Evans, J., Bell, P., Thompson, M., 2005. HMG-CoA reductase inhibitors (statins) decrease MMP-3 and MMP-9 concentrations in abdominal aortic aneurysms. *Eur. J. Vasc. Endovasc. Surg.* 30 (3), 259–262.
- Steinmetz, E.F., Buckley, C., Shames, M.L., Ennis, T.L., Vanvickie-Chavez, S.J., Mao, D., et al., 2005. Treatment with simvastatin suppresses the development of experimental abdominal aortic aneurysms in normal and hypercholesterolemic mice. *Ann. Surg.* 241 (1), 92.
- Kalyanasundaram, A., Elmore, J.R., Manazer, J.R., Golden, A., Franklin, D.P., Galt, S.W., et al., 2006. Simvastatin suppresses experimental aortic aneurysm expansion. *J. Vasc. Surg.* 43 (1), 117. -e39.
- Kopacz, A., Werner, E., Grochot-Przeczek, A., Klóska, D., Hajduk, K., Neumayer, C., et al., 2020. Simvastatin attenuates abdominal aortic aneurysm formation favoured by lack of Nrf2 transcriptional activity. *Oxid. Med. Cell. Longev.* 2020.
- Ma, H., Liang, W.-J., Shan, M.-R., Wang, X.-Q., Zhou, S.-N., Chen, Y., et al., 2017. Pravastatin activates activator protein 2 alpha to augment the angiotensin II-induced abdominal aortic aneurysms. *Oncotarget* 8 (9), 14294.
- Shiraya, S., Miyake, T., Aoki, M., Yoshikazu, F., Ohgi, S., Nishimura, M., et al., 2009. Inhibition of development of experimental aortic abdominal aneurysm in rat model by atorvastatin through inhibition of macrophage migration. *Atherosclerosis* 202 (1), 34–40.
- Wang, J.-A., Chen, W.-A., Wang, Y., Zhang, S., Bi, H., Hong, B., et al., 2011. Statins exert differential effects on angiotensin II-induced atherosclerosis, but no benefit for abdominal aortic aneurysms. *Atherosclerosis* 217 (1), 90–96.
- Li, Y., Lu, G., Sun, D., Zuo, H., Wang, D.W., Yan, J., 2017. Inhibition of endoplasmic reticulum stress signaling pathway: a new mechanism of statins to suppress the development of abdominal aortic aneurysm. *PLoS One* 12 (4), e0174821.
- Houdek, K., Moláček, J., Třeška, V., Krížková, V., Eberlová, L., Boudová, L., et al., 2013. Focal histopathological progression of porcine experimental abdominal aortic aneurysm is mitigated by atorvastatin. *Int. Angiol.* 32 (3), 291–306.
- Katsuki, S., Koga, J.-i., Matoba, T., Umezū, R., Nakashiro, S., Nakano, K., et al., 2021. Nanoparticle-mediated delivery of pitavastatin to monocytes/macrophages inhibits angiotensin II-induced abdominal aortic aneurysm formation in ApoE^{-/-}Mice. *J. Atheroscler. Thromb.* 54379.
- Nagashima, H., Aoka, Y., Sakomura, Y., Sakuta, A., Aomi, S., Ishizuka, N., et al., 2002. A 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, cerivastatin, suppresses production of matrix metalloproteinase-9 in human abdominal aortic aneurysm wall. *J. Vasc. Surg.* 36 (1), 158–163.
- Evans, J., Powell, J., Schwalbe, E., Loftus, I., Thompson, M., 2007. Simvastatin attenuates the activity of matrix metalloproteinase-9 in aneurysmal aortic tissue. *Eur. J. Vasc. Endovasc. Surg.* 34 (3), 302–303.
- Karrowin, W., Dughman, S., Hajj, G.P., Miller, F.J., 2011. Statin therapy reduces growth of abdominal aortic aneurysms. *J. Invest. Med.* 59 (8), 1239–1243.
- Nemoto, M., Hoshina, K., Takayama, T., Miura, S., Nakazawa, T., Kato, M., et al., 2013. Statins reduce extensive aortic atheromas in patients with abdominal aortic aneurysms. *Ann. Vasc. Dis.* 0a13-00065.
- Mathisen, S.R., Abdelnoor, M., 2017. Beneficial effect of statins on total mortality in abdominal aortic aneurysm (AAA) repair. *Vasc. Med.* 22 (5), 406–410.
- O'Donnell, T.F., Deery, S.E., Shean, K.E., Mittleman, M.A., Darling, J.D., Esлами, M.H., et al., 2018. Statin therapy is associated with higher long-term but not perioperative survival after abdominal aortic aneurysm repair. *J. Vasc. Surg.* 68 (2), 392–399.
- Yoshimura, K., Nagasawa, A., Kudo, J., Onoda, M., Morikage, N., Furutani, A., et al., 2015. Inhibitory effect of statins on inflammation-related pathways in human abdominal aortic aneurysm tissue. *Int. J. Mol. Sci.* 16 (5), 11213–11228.
- Takagi, H., Yamamoto, H., Iwata, K., Goto, S., Umamoto, T., Group, A., 2012. Effects of statin therapy on abdominal aortic aneurysm growth: a meta-analysis and meta-regression of observational comparative studies. *Eur. J. Vasc. Endovasc. Surg.* 44 (3), 287–292.
- Twine, C., Williams, I., 2011. Systematic review and meta-analysis of the effects of statin therapy on abdominal aortic aneurysms. *Br. J. Surg.* 98 (3), 346–353.
- van der Meij, E., Koning, G.G., Vriens, P.W., Peeters, M.F., Meijer, C.A., Kortekaas, K.E., et al., 2013. A clinical evaluation of statin pleiotropy: statins selectively and dose-dependently reduce vascular inflammation. *PLoS One* 8 (1), e53882.
- Daugherty, A., Cassis, L.A., Lu, H., 2011. Complex pathologies of angiotensin II-induced abdominal aortic aneurysms. *J. Zhejiang Univ. Sci. B* 12 (8), 624–628.
- Loboda, A., Damulewicz, M., Pyza, E., Jozkowicz, A., Dulak, J., 2016. Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionarily conserved mechanism. *Cell. Mol. Life Sci.* 73 (17), 3221–3247.
- Choi, S.H., Park, S., Oh, C.J., Leem, J., Park, K.-G., Lee, I.-K., 2015. Dipeptidyl peptidase-4 inhibition by gemigliptin prevents abnormal vascular remodeling via NF-E2-related factor 2 activation. *Vasc. Pharmacol.* 73, 11–19.
- Ruotsalainen, A.-K., Inkala, M., Partanen, M.E., Lappalainen, J.P., Kansanen, E., Mäkinen, P.I., et al., 2013. The absence of macrophage Nrf2 promotes early atherogenesis. *Cardiovasc. Res.* 98 (1), 107–115.
- Song, H., Xu, T., Feng, X., Lai, Y., Yang, Y., Zheng, H., et al., 2020. Itaconate prevents abdominal aortic aneurysm formation through inhibiting inflammation via activation of Nrf2. *EBioMedicine* 57, 102832.
- Klóska, D., Kopacz, A., Piechota-Polanczyk, A., Nowak, W.N., Dulak, J., Jozkowicz, A., et al., 2019. Nrf2 in aging—Focus on the cardiovascular system. *Vasc. Pharmacol.* 112, 42–53.
- Yeh, Y.-H., Kuo, C.-T., Chang, G.-J., Chen, Y.-H., Lai, Y.-J., Cheng, M.-L., et al., 2015. Rosuvastatin suppresses atrial tachycardia-induced cellular remodeling via Akt/Nrf2/heme oxygenase-1 pathway. *J. Mol. Cell. Cardiol.* 82, 84–92.
- Ma, Y., Chen, Z., Zou, Y., Ge, J., 2014. Atorvastatin represses the angiotensin 2-induced oxidative stress and inflammatory response in dendritic cells via the PI3K/Akt/Nrf 2 pathway. *Oxid. Med. Cell. Long.* 2014.
- Araujo, J.A., Zhang, M., Yin, F., 2012. Heme oxygenase-1, oxidation, inflammation, and atherosclerosis. *Front. Pharmacol.* 3, 119.
- Azuma, J., Wong, R.J., Morisawa, T., Hsu, M., Maegdefessel, L., Zhao, H., et al., 2016. Heme oxygenase-1 expression affects murine abdominal aortic aneurysm progression. *PLoS One* 11 (2), e0149288.
- Hsu, M., Muchova, L., Morioka, I., Wong, R.J., Schröder, H., Stevenson, D.K., 2006. Tissue-specific effects of statins on the expression of heme oxygenase-1 *in vivo*. *Biochem. Biophys. Res. Commun.* 343 (3), 738–744.
- Lee, T.-S., Chang, C.-C., Zhu, Y., Shyy, J.Y.-J., 2004. Simvastatin induces heme oxygenase-1: a novel mechanism of vessel protection. *Circulation* 110 (10), 1296–1302.
- Sakalihan, N., Delvenne, P., Nusgens, B.V., Limet, R., Lapière, C.M., 1996. Activated forms of MMP2 and MMP9 in abdominal aortic aneurysms. *J. Vasc. Surg.* 24 (1), 127–133.
- Crowther, M., Goodall, S., Jones, J.L., Bell, P.R., Thompson, M.M., 2000. Increased matrix metalloproteinase 2 expression in vascular smooth muscle cells cultured from abdominal aortic aneurysms. *J. Vasc. Surg.* 32 (3), 575–583.
- Molloy, K.J., Thompson, M.M., Schwalbe, E.C., Bell, P.R., Naylor, A.R., Loftus, I.M., 2004. Comparison of levels of matrix metalloproteinases, tissue inhibitor of metalloproteinases, interleukins, and tissue necrosis factor in carotid endarterectomy specimens from patients on versus not on statins preoperatively. *Am. J. Cardiol.* 94 (1), 144–146.
- Miller Jr, F.J., Sharp, W.J., Fang, X., Oberley, L.W., Oberley, T.D., Weintraub, N.L., 2002. Oxidative stress in human abdominal aortic aneurysms: a potential mediator of aneurysmal remodeling. *Arterioscler. Thromb. Vasc. Biol.* 22 (4), 560–565.
- Diehm, N., Dick, F., Schaffner, T., Schmidli, J., Kalka, C., Di Santo, S., et al., 2007. Novel insight into the pathobiology of abdominal aortic aneurysm and potential future treatment concepts. *Prog. Cardiovasc. Dis.* 50 (3), 209–217.
- Piechota-Polanczyk, A., Goraca, A., Demyanets, S., Mittlboeck, M., Domenig, C., Neumayer, C., et al., 2012. Simvastatin decreases free radicals formation in the human abdominal aortic aneurysm wall via NF-κB. *Eur. J. Vasc. Endovasc. Surg.* 44 (2), 133–137.
- Lee, J.K., Borhani, M., Ennis, T.L., Upchurch Jr, G.R., Thompson, R.W., 2001. Experimental abdominal aortic aneurysms in mice lacking expression of inducible nitric oxide synthase. *Arterioscler. Thromb. Vasc. Biol.* 21 (9), 1393–1401.
- Johanning, J.M., Armstrong, P.J., Franklin, D.P., Han, D.C., Carey, D.J., Elmore, J.R., 2002. Nitric oxide in experimental aortic aneurysm formation: early events and consequences of nitric oxide inhibition. *Ann. Vasc. Surg.* 16 (1), 65–72.
- Zhang, J., Schmidt, J., Ryschich, E., Mueller-Schilling, M., Schumacher, H., Allenberg, J.R., 2003. Inducible nitric oxide synthase is present in human abdominal aortic aneurysm and promotes oxidative vascular injury. *J. Vasc. Surg.* 38 (2), 360–367.
- Adams, L., Brangsch, J., Hamm, B., Makowski, M.R., Keller, S., 2021. Targeting the extracellular matrix in abdominal aortic aneurysms using molecular imaging insights. *Int. J. Mol. Sci.* 22 (5), 2685.

- Hellenthal, F.A., Buurman, W.A., Wodzig, W.K., Schurink, G.W.H., 2009. Biomarkers of AAA progression. Part 1: extracellular matrix degeneration. *Nat. Rev. Cardiol.* 6 (7), 464.
- Xiong, W., MacTaggart, J., Knispel, R., Worth, J., Persidsky, Y., Baxter, B.T., 2009. Blocking TNF- α attenuates aneurysm formation in a murine model. *J. Immunol.* 183 (4), 2741–2746.
- Krysiak, R., Gdula-Dymek, A., Ścieszka, J., Okopień, B., 2011. Anti-inflammatory and monocyte-suppressing effects of simvastatin in patients with impaired fasting glucose. *Basic Clin. Pharmacol. Toxicol.* 108 (2), 131–137.
- Shen, Y., Wu, H., Wang, C., Shao, H., Huang, H., Jing, H., et al., 2010. Simvastatin attenuates cardiopulmonary bypass-induced myocardial inflammatory injury in rats by activating peroxisome proliferator-activated receptor γ . *Eur. J. Pharmacol.* 649 (1–3), 255–262.
- Hurks, R., Hofer, I.E., Vink, A., Pasterkamp, G., Schoneveld, A., Kerver, M., et al., 2010. Different effects of commonly prescribed statins on abdominal aortic aneurysm wall biology. *Eur. J. Vasc. Endovasc. Surg.* 39 (5), 569–576.
- Wang, S., Kaufman, R.J., 2012. The impact of the unfolded protein response on human disease. *J. Cell Biol.* 197 (7), 857–867.
- Hotamisligil, G.S., 2010. Endoplasmic reticulum stress and atherosclerosis. *Nat. Med.* 16 (4), 396–399.
- Hotamisligil, G.S., 2010. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 140 (6), 900–917.
- Bahrami A, Parsamanesh N, Atkin SL, Banach M, Sahebkar A. Effect of statins on toll-like receptors: a new insight to pleiotropic effects. *Pharmacol. Res.* 2018 Sep;135:230-238. doi: 10.1016/j.phrs.2018.08.014. Epub 2018 Aug 16. PMID: 30120976.
- Bahrami A, Bo S, Jamialahmadi T, Sahebkar A. Effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on ageing: Molecular mechanisms. *Ageing Res. Rev.* 2020 Mar;58:101024. doi: 10.1016/j.arr.2020.101024. Epub 2020 Jan 30. PMID: 32006687.