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# Resistance of Statin Therapy, and Methods for its Influence

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Additional information is available at the end of the chapter

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## 1. Introduction

Resistance happens when an individual has an incorrect response to the effectiveness of a drug as stated in the National Library of Medicine. It is difficult to give an accurate definition of statin resistance. Patients who fail to reach LDL-C target levels despite undergoing the best available therapy of the most highly tolerated dose of a more potent statin, are considered to be statin-resistant. Many individuals do not reach LDL-C target levels, even when compliance is taken into consideration. The reduction of LDL-C in response to statin therapy can vary from 5-70 %. This can be influenced by many factors. For instance, racial and ancestry, with attenuated responses in blacks compared to whites. A study comparing statin resistance patients to patients who show no resistance to statin has yet to appear.

The resistance to statins can be related to differences in drug absorption, drug transport, intrahepatic drug metabolism, drug metabolism within other organs, and drug excretion mechanisms. The same can occur due to differences in the level of the various target pathways that are unrelated to pharmacokinetics, including HMG-CoA reductase, as well as various points along the cholesterol biosynthesis and lipoprotein metabolic pathways.

## 2. Possible causes of statin resistance

According to Herman and Moncada the process of atherogenesis includes 28 stages. [48] Key points in this process are two - oxygenated LDL-cholesterol and endogenous nitric oxide synthase. Statin resistance may exist in both directions:

### 2.1. Failed targeting LDL cholesterol

It seems that not only genetic but environmental factors can influence the LDL-C response to statins. Studies have found that patients with hypertension have a smaller decrease than those without hypertension. Furthermore, smokers have smaller statin-induced LDL-C decrease compared with nonsmokers[47]. It also seems that inflammation might cause statin resistance. Namely, it has been shown that inflammatory cytokines, in particular IL-1 $\beta$  which affects sterol regulatory element binding protein cleavage-activating protein, cause statin resistance due to the disruption of LDL-R feedback regulation. Therefore, it has been suggested that in inflammatory states, higher concentrations of statin may be required to achieve the appropriate LDL-C lowering [107]. Particularly interesting are observations concerning certain subpopulations of patients who might be resistant to statin treatment. Some studies have shown statins to be less effective in individuals with HIV infection. [22]. Other studies have a contraversal perspective. [55]. The role of concomitant amiodarone treatment in statin resistance was also suspected. Both amiodarone and amiodarone induced hypothyroidism influence the synthesis of LDLR, which may explain the lack of statin effect. Thyroid hormone is one of several hormones that control gene expression of the LDLR and hypothyroidism is a wellknown cause of secondary dyslipidemia characterized by elevated LDL-C levels. Similar to hypothyroidism, administration of amiodarone also increases LDL-C levels, which is the result of a decreased expression of the LDLR gene [1].

More recently, an approach was published which used metabolomics to identify markers indicative of mechanisms that contribute to differences in LDL-C response to statin. Metabolic changes were shown to be more comprehensive in responders to statin treatment than those seen in nonresponders. The baseline cholesterol ester and phospholipid metabolites correlated with LDL-C response to treatment [56]. It has also been suggested that clusters of metabolites involved in multiple pathways not directly connected with cholesterol metabolism might as well play a role in modulating the response to statin therapy - influence statin resistance [90].

Insufficient LDL-C response to statin treatment is probably the result of pseudo-resistance, which could be caused by nonadherence or nonpersistence in real life circumstances. [68].

### 3. Lack of effect on the endothelium-dependent vasodilation after targeting LDL-C

There is a lot of evidence that the endothelium plays a crucial role in the maintenance of vascular tone and structure. [39; 40, 41; 38; 5; 51; 9]. One of the major endothelium-derived vasoactive mediators was shown to be nitric oxide (NO). [38; 74; 51; 67]. Multifunctional are the mechanism by which NO activity is reduced: reduced NO release, NO inactivation by superoxide anion, or reduced NO production by NO synthase (NOS). [91] Decrease in NOS expression by oxidized low-density lipoprotein (LDL) can cause impaired NO production [77; 91], or by the presence of asymmetric dimethylarginine (ADMA). [72; 16 ;29]

According to Herman and Moncada the basis of atherogenesis remain oxygenated LDL and eNOS. Lipid-regulating effects of statins in terms of LDL-cholesterol are undeniable, but the

pleiotropic dysfunction is a particularly relevant issue of resistance of statin therapy in patients with high levels of ADMA - endogenous inhibitor of eNOS. Research of statin influence on flow-mediated vasodilation (FMD) reveals controversial results. Some studies indicate that there is an effect, whereas others document the opposite tendency [18]. There is a number of studies on simvastatin and likewise they demonstrate controversial findings. These controversies can be dismissed by studying ADMA levels. [18; 16; 6]. It has been suggested that ADMA could modify the effect of statins on myocardial blood flow and on FMD% [53].

In our subsequent studies found in a logical sequence following facts. This facts determinate ADMA as a basic factor for statin's resistans.

International recommendations underline the importance of diagnosis and treatment of asymptomatic individuals with high absolute cardiovascular risk [10; 37; 8], as individuals with severe hypercholesterolemia. [47; 45; 58] the levels of ADMA in patients with severe hypercholesterolemia in our study are higher than those cited in the literature in the same population patients. [13].

1. A good marker of endothelial dysfunction is considered to be ADMA, as indicated by recent publications. [16]. Subjects with cardiovascular risk – hypercholesterolemia, hyperhomocysteinemia, diabetes mellitus, hypertension, smoking, erectile dysfunction having increased ADMA levels. [67; 11; 16,17]. Plasma levels of ADMA have been shown to be elevated in hypercholesterolemic rabbits [108]. The elevation of ADMA is associated with reduced activity of NOS in animal models, as well as in young asymptomatic hypercholesterolemic adults [13]. The mechanism of increased ADMA in hypercholesterolemia is not very clear - LDL cholesterol increases the expression of ADMA precursor protein and reduces the activity of the enzyme dimethyl arginine dimethyl amino hydrolase. [52; 15] Increased ADMA are associated with reduced NO synthesis and this assessed by impaired endothelium-dependent vasodilatation. Flow-mediated dilatation (FMD) - shear stress during hyperemia activates receptors on the endothelial cell surface and causes influx of intracellular calcium, which activates eNOS and NO release [54; 24; 80; 60]. The main effect that dilatation has in respons to shear stress during FMD is influenced by NO and to a smaller extent on prostaglandins and endothelial-dependent hyperpolarizing factors [78; 54; 31; 30; 73]. Ultrasound determination of flow-mediated dilatation of the brachial artery as a method has many advantages – it is non-invasive, with good reproducibility and reliable. [3; 28; 31; 36; 61]. There is convincing evidence that reduced percentage of FMD (FMD%) is a marker of coronary endothelial dysfunction [3].

Several studies have associated hypercholesterolemia with reduced FMD% and this effect can be reversed by L-arginine [34; 26; 32; 33]. However, L-arginine does not lead to the improvement of endothelial dependent vasodilatation in normocholesterolemic individuals. In this condition indicate the main role of endogenous ADMA. [11; 44] Furthermore, a recent publication demonstrated that improvement of FMD% under statin treatment depends on the ADMA levels [53; 12]. Little is know about the relationship between ADMA, and FMD%. In a small number of hypercholesterolemic patients ADMA was shown to be positively correlated with FMD% in mild hypercholesterolemia [13]. A recent paper demonstrated that low cardiovascular risk subjects have increased ADMA level. [6]. No data exist about the relationship between ADMA and FMD% in severe hypercholesterolemia patients. In our study

"Relationship of asymmetric dimethylarginine with flow-mediated dilatation in subjects with newly detected severe hypercholesterolemia" was the evaluation of the relationship between ADMA and FMD, also that of ADMA and lipid parameters as well as other endothelial dysfunction in newly detected subjects with severe hypercholesterolemia. The major findings of the present study are that: (1) plasma levels of ADMA, are increased in severe hypercholesterolemia; (2) there is a significant link between ADMA and age, Apo-B, Apo-B/Apo-A<sub>1</sub> and tHcy; (3) newly detected severe hypercholesterolemia has reduced flow-mediated endothelial dependent vasodilatation, there is a correlation between plasma levels of FMD% and age, Apo-B, Apo-B/Apo-A<sub>1</sub> and tHcy; and (4) homocystein levels has no contribution to the atherogenic risk in the patients.

Newly detected severe hypercholesterolemia is associated with elevated ADMA, and to the proportional increase in total cholesterol. The ADMA correlates with age, Apolipoprotein-B, Apo-B/Apo-A<sub>1</sub> and tHcy. Apo-B was found to indicate elevated ADMA in these patients. FMD % correlates most strongly with age, Apolipoprotein-B, index Apo-B/Apo-A<sub>1</sub> and tHcy. In multiple regression analysis, ADMA is the strongest predictor for FMD%. ADMA is the main modulator of FMD% - among the investigated biomarkers in newly detected severe hypercholesterolemia. Serious functional changes in the vascular wall are cause by increased level of ADMA. At the same time, ADMA is found to be a predictor of flow-modulated vasodilation of the brachial artery which also makes a probable marker for endothelial dysfunction. Therefore, measuring ADMA levels in newly detected severe hypercholesterolemia is of great importance when FMD% changes need to be clarified.

2. In the next study we investigated intima-media complex of carotid artery. The intima-media thickness (IMT) of the CCA is one of the validated measurements of subclinical atherosclerosis, as early as structural vascular abnormalities [85]. Intima-media thickening of the CCA correlates with the coronary risk factors [80] and with associated with the degree of coronary atherosclerosis. It serves as a predictor of coronary and vascular events in different patients' populations. Intima-media thickening reflects both intimal atherosclerosis and medial hypertrophy. It is used to evaluate the luminal and wall characteristics of the carotid artery. In the literature, hypercholesterolemia has an important role in early-onset IMT changes in the CCA However, there is not a lot of data about asymptomatic subjects with newly detected severe hypercholesterolemia.[72]. In the literature, data on the IMT of CCA predictors is controversial. There are a few studies of the endothelium-related biomarkers (ADMA, tHcy, soluble cell adhesion molecules), especially in asymptomatic subjects with newly detected severe hypercholesterolemia [72].

The research "Predictors of the intima-media thickness of carotid artery in asymptomatic newly detected severe hypercholesterolemic patients" age and Apo-B were established as the most important statistically significant factors related to IMT mean of CCA. This fact illustrates that they determine the slow progressive structural changes in the vascular wall. The Apo-B is a better biomarker of the total number of atherogenic particles. It might be concluded that Apo-B is a better factor for assessment of risk, as LDL cholesterol underestimates the risk in asymptomatic subjects with newly detected severe hypercholesterolemia.

In the study "Intima-Media Thickness and Flow-Mediated Vasodilation in Asymptomatic Subjects with Newly Detected Severe Hypercholesterolemia", our results show a significant correlation between IMT mean and FMD%. The correlation is still present when separating IMT on the basis of the level of thickening. This supports the idea that the two noninvasive methods complete each other. It is important with regard to building a diagnostic algorithm. These methods show early subclinical atherosclerosis but by different trigger mechanisms.

3. After establishing who is a predictor of FMV - ADMA, the next study proved that ADMA is the main determinant of the effect of simvastatin on FMV in severe hypercholesterolemia - "Asymmetric dimethylarginine determines the effect of simvastatin on endothelium-dependent vasodilation in severe hypercholesterolemia" *Future Medicine Clinical Lipidology* 2010. With respect to their total cholesterol, LDL-cholesterol and FMD% the two groups of hypercholesterolemic patients (according to the plasma ADMA levels) differ significantly. ADMA, cell adhesion molecules or total homocysteine levels are not affected by Simvastatin in moderate dose [40 mg). Higher baseline levels of ADMA affect the ability of statins to improve endothelium-dependent vasodilation by diminishing it. Subjects from the same population, but with lower baseline levels of ADMA experience the same effect of simvastatin. Therefore, ADMA seems to be a pathophysiological modulator of the statin therapeutic response. The present study has been confirmed by studies that there is a connection between ADMA and FMD% response to statins found by Böger et al. The difference is that in our study is in the larger group of the patients.

In terms of non-randomized study "Effect of Moderate and High-Dose Simvastatin on Asymmetric-Homocysteine Metabolic Pathways in Patients with Newly Detected Severe Hypercholesterolemia" was demonstrated dose-dependent effect of simvastatin on the levels of ADMA. The 40 mg simvastatin has no effect on ADMA and homocysteine level in contrast to 80 mg, after target LDL-levels are reached  $\leq 2.6$  mmol/L. It is likely that statin-pleiotropic effects on ADMA-homocysteine metabolic pathways are independent of their lipid-regulating properties.

In another of our observations "Asymmetric dimethylarginine-a determinant of the effect of the high dose Simvastatin confirmed this dose-dependent effect". The two groups of patients (according to the plasma ADMA levels) differ significantly with respect to their total cholesterol, LDL-cholesterol and FMD%. Simvastatin in moderate dose (40 mg) does not affect ADMA, cell adhesion molecules and total homocysteine levels. The higher levels of ADMA change the ability of statins to improve the endothelium-dependent vasodilation, by diminishing it. This shows that ADMA is a pathophysiological modulator of the statin therapeutic response. This study confirms that, for the first time, there is a correlation between ADMA levels and FMD% response to statins, found by Böger et al., but in the larger group of patients with severe hypercholesterolemia and with higher dose simvastatin. Obviously, these mechanisms require further investigation

To give a more precise answer to the question of dose-dependent manner for avoidable statin resistance subsequently conducted a randomized, placebo-controlled study "The effect of simvastatin on asymmetric dimethylarginine and flow-mediated vasodilation after optimizing the LDL level — A randomized, placebo-controlled study" The major findings of the present

study are 1. Significantly higher ADMA and tHcy were seen in patients with severe hypercholesterolemia compared to the control group. 2. Administration of 40 mg simvastatin for one month results in no variation in ADMA, tHcy plasma levels and FMD%, following optimizing of the LDL. 3. Administration of 80 mg simvastatin for a month leads to a variation of ADMA and tHcy plasma levels and FMD% after optimizing the LDL. FMD%-changes can be predicted with ADMA levels and ApoB%-changes is a predictor of LDL-changes% in patients on 80 mg simvastatin (for one month) following the optimization of the LDL-C.

This study gives evidence that in experimental models and in humans (59), higher ADMA levels have a harmful effect on the coronary endothelium. On the other hand, the experimental model shows that statins have no protective effect against that harmful effect of ADMA on the endothelium. This provokes a discussion as to whether ADMA is the pathophysiological modulator of the therapeutic response of statins in hypercholesterolemia.

The ADMA in severe hypercholesterolemia are higher compared to those in patients in similar research protocols (13), and are similar to those in our previous research studies. Applying various laboratory methods (ELISA in the present study, high-pressure liquid chromatography in other studies) does not allow for the mean levels of ADMA to be compared directly. Using ELISA to differentiate the sample groups is less reliable than LC-MS. This is caused by the fact that the higher coefficient of variation and to the fact that the matrix dependence is likely to cloud or mimic the differences. The ADMA ELISA method can be used for clinical investigations in which groups of samples are compared and the result is the shift of the ADMA concentration in response to an intervention. The application of ELISA analysis in our study is the likely explanation of the higher levels of ADMA, in comparison with other studies (13). On the other hand, this is likely due to the higher levels of total cholesterol  $> 7.5$  mmol/l and LDL-C  $> 4.9$  mmol/l. The difference in L-arginine substitution in hypercholesterolic patients and normo-cholesterolic patients is explained by the higher levels of ADMA in hypercholesterolic patients in comparison with controls with controls (11; 44).

The mechanism of an increased ADMA level in hypercholesterolemia is not clear enough. An association between ADMA and hypercholesterolemia has been previously observed [13]. Laufs et al. (1998) demonstrated that simvastatin reverse, in a dose-dependent manner, the inhibitory effect of oxidized LDL on NO production. It has been suggested that LDL-cholesterol increases the expression of ADMA precursor protein. This reduces the activity of the enzyme dimethylarginine dimethylaminohydrolase, which breaks down ADMA [52]. This is why, by decreasing cholesterol levels with statin therapy, ADMA plasma levels will decrease as well. The therapeutic hypothesis that the decrease of circulating ADMA levels can be achieved by lowering plasma cholesterol levels is the main idea in this publication.

In randomized, placebo-controlled research, a statistically significant reduction of ADMA plasma levels has been established following a one-month therapy with 80 mg simvastatin, yet the 40 mg simvastatin dose does not result in achieving the LDL target levels. The study showed that a 40 mg simvastatin therapy for 3 months does not produce the desired effect. Therefore, it is likely that the pleiotropic effect of the statins (respectively ADMA and tHcy) is independent from the lipid-regulation in a short-term and long-term plan. The lack of effect on 40 mg simvastatin coincides with the results presented in other studies but there is no

optimizing of LDL-C level. The research in similar articles regarding the effect of 80 mg simvastatin on ADMA levels is scant. Most research works have documented a negative effect in hypercholesterolemia. However, these studies have tested a considerably smaller number of patients (64). The present study comprises 85 patients and LDL target levels have been optimized regarding the risk category. The established statistically significant therapeutic effect of 80 mg simvastatin on ADMA is comparable to the results from a recently published study – an experimental model of the effect of simvastatin on ADMA tissue levels (64). This recent experimental data shows that simvastatin regulates dimethylarginine dimethylaminohydrolase transcription via the transcription factor Sterol Regulatory Element Binding Protein. The latter is activated by statins due to a reduction of plasma membrane cholesterol. These experimental models suggest that the level of asymmetric dimethylarginine will be decreased by statin therapy. Almost all other clinical studies (of smaller sample size and shorter duration) showed no effect of statins on ADMA (positive effect only 10 mg rosuvastatin and 80 mg fluvastatin). It is unclear whether the higher plasma levels of ADMA in human disease states correlate with a higher intracellular level. Studies testing the statin effect in vivo have reported endothelial protection without overly affecting plasma ADMA levels, however in these studies the tissue levels of ADMA have not been taken into consideration. It is likely that in the present study achieving the LDL-C target level substitutes for the LDL-cholesterol tissue levels. Similar titrations have not been carried out in any other related articles so far. The results of the present study provide further clinical evidence to the experimental model of the Ivashchenko et al., that simvastatin regulates dimethylarginine dimethylaminohydrolase transcription via the transcription factor Sterol Regulatory Element Binding Protein.

The present study shows a statistically significant increase in FMD% in patients on 80 mg simvastatin therapy for one month in the presence of controversial results in related materials on this issue. The mechanism of this improvement is proved to be related to the enhancement of gene expression of eNOS (64). On the other hand, the FMD%-changes correlate (correlations with all biomarkers at a baseline level and the %-changes have been tested) significantly only with the baseline level of ApoB, ADMA, and tHcy. Interestingly enough, patients with ADMA levels greater than 1  $\mu\text{mol/l}$ , following statin therapy, appear to have only small or no FMD% changes. A likely explanation of this finding is that in patients with ADMA greater than 1  $\mu\text{mol/l}$ , competes with L-arginine as a substrate for eNOS and thus decreases the production and availability of endothelium-derived NO. For this reason, in such patients, there are no FMD% changes following statin therapy. In patients with documented small FMD% changes, the most likely explanation is the action of other mediators (endothelium-derived hyperpolarizing factor or prostaglandins) that lead to vasodilation through calcium-activated potassium channels simvastatin (80 mg daily).

The high simvastatin doses should be done with caution. According to the Food and Drug Administration monitoring are also important every 3 and 6 months during the course of therapy.

In the multifactor regressive analysis only the initial ADMA levels remain predictors of an FMD%-change. For the first time, in 2007 Böger GI et al. established that ADMA determines FMD%- changes in a small hypercholesterolemic patients group (treated with a smaller



simvastatin dose — 40 mg (12). Further clinical studies can be based off of this study, in order to achieve LDL-target levels and to optimize the effect of different doses statins on ADMA. Other statins are better tolerated at a high dose (atorvastatin, pravastatin, fluvastatin, lovastatin). There is only one study testing the effect of 80 mg fluvastatin treatment in hypercholesteremic patients with metabolic syndrome, which demonstrated decrease in plasma ADMA level at 6 weeks.

What is interesting is that the established fact that the Apo-B%-change (not the LDL%-change) is a predictor of the changes in the plasma levels of ADMA (ADMA%-change) in the linear regression model. It's very likely that this is due to the level of the smallest atherogenic and dense particles are reflected by ApoB. The fact that ApoB is a predictor of the ADMA%-change presumably is due to the higher proportion of patients with family Apo B defect (previously reported in patients with hypercholesterolemia in our previous studies).

Statins vary in their pharmacokinetics and pharmacodynamics. There is a difference in their lipid regulating and pleiotropic effect. Therefore, the data on simvastatin could not be referred to other statins. There is no other therapeutic option in cases with high ADMA levels in hypercholesteremic patients, apart from 80 mg simvastatin. The clinical significance of our study is that high-risk patients with severe hypercholesterolemia, a family history of premature atherosclerosis and a high level of plasma ADMA, the high dose of Simvastatin is a possible therapeutic option. Substituting with L-arginine is another possible approach (11; 44; 92). These two hypotheses complete one another.

A number of factors are the cause of controversial results on the effects of statins on the endothelial-dependent vasodilation. 1. The clinical studies, testing the effect of statins on ADMA and FMD% involve only a small number of patients for a short period of time. 2. LDL levels are not optimized in accordance with the risk category of hypercholesteremic patients (the pleiotropic effects of statins are partly connected to lipid regulating ones). 3. The improvement of FMD% via increasing the activity of NO with the statin therapy is connected additionally to the effect on other inhibitors of eNOS apart from ADMA. 4. In most studies there is no testing of ADMA tissue levels.

The present study established patients with severe hypercholesterolemia have high ADMA levels in comparison with the control group. One-month treatment with 80 mg simvastatin, aimed at achieving LDL target levels of  $\leq 2.6$  mmol/l in high-risk contingents with severe hypercholesterolemia leads to a statistically significant reduction of ADMA and an increase of FMD% in contrast with 40 mg simvastatin therapy. The FMD%-changes correlate in a statistically significant way with the initial ApoB, ADMA and tHcy levels. The baseline ADMA levels are a predictor of FMD% changes and Apo-B%-changes is a predictor of ADMA%-changes at baseline and post one-month therapy with 80 mg simvastatin. In case of optimized LDL target levels it appears that ADMA is a major modulator of FMD%-change.

#### **4. The impact of genetic factors on statin resistance**

The same dose of the same statin in different individuals produces different LDL-C decreases. The time to reach maximum LDL-C decrease differs significantly between individuals. [81;

82] Such a wide interindividual variation as the response to statins is more and more attributed, at least partly, to the polymorphisms in genes affecting statin pharmacodynamics and pharmacokinetics. The resistance to statins has been associated with polymorphisms in the HMG-CoA-R, ABCB1, ABCG2, ABCC1, ABCC2, OATP1B1, OATP2B1, RHOA, NPC1L1, FXR, CYP7A1, ApoE, PCSK9, LDLR, LPA, CETP, and TNF- $\alpha$  genes. However, currently, there is still not enough evidence to advocate pharmacogenetic testing before initiating therapy with statins.

Pharmacogenetics seeks to determine the role of genetic factors in variation of statin response. However, today the origins of the notable interindividual variation in response to statins are still poorly understood. In a number of studies, genetic variability has been shown to affect statin responsiveness thus influencing statin resistance. These studies have identified numerous candidate genes (>50) and dozens of single-nucleotide polymorphisms (SNPs). It has been reported to be associated with differing aspects of statin response - pharmacokinetics and pharmacodynamics of statins being potential determinants of drug responsiveness in terms of LDL-C lowering. Although genes are supposed to be associated with statin cholesterol-lowering efficacy, the magnitude of variation in statin response that could be explained by these associations is still questionable. [62; 89; 35; 79; 71]

The association between SNPs in genes involved in lipid metabolism and total cholesterol and LDL-C response to statin therapy is of particular interest. The 3-hydroxyl-3-methylglutaryl coenzyme A reductase (HMG-CoA-R) gene encoding the enzyme HMG-CoA-R, which is the principal target of statins, because the foremost pharmacological action of these drugs is exactly the competitive inhibition of HMG-CoA-R. The last one might be one of the candidate genes when analyzing the SNPs as a possible cause of diminished statin responsiveness. When SNPs and the common haplotypes inferred from them were tested for association with plasma LDL-C levels and LDL-C response to statin treatment, it has been shown that HMG-CoA-R gene polymorphisms are associated with reduced plasma LDL-C levels and LDL-C response to simvastatin. [104; 42; 75; 84; 88; 49; 50]

Therefore, although it was considered that genome-wide association studies may yield a more comprehensive set of markers for predicting statin efficacy and/or resistance, this has not been proven so far and the results of these studies cannot be translated into clinical practice yet. We need future pharmacogenetic research [93].

## 5. Conclusion

It is difficult to give an accurate definition of statin resistance. The patients who fail to reach LDL-C target values despite the best available therapy, mostly a highest tolerable dose of a more potent statin, are considered to be statin-resistant. Resistance to statins can be related to differences in drug absorption, transport, intrahepatic drug metabolism, drug metabolism within other organs, and drug excretion mechanisms. Possible causes of statin resistance: **1. Failed targeting LDL cholesterol** - smokers have smaller statin-induced LDL-C decrease compared with nonsmokers and the patients with hypertension have smaller decrease than

those without hypertension, inflammation might cause statin resistance. The role of concomitant amiodarone treatment in statin resistance was also suspected. It has also been suggested that clusters of metabolites involved in multiple pathways not directly connected with cholesterol metabolism might as well play a role in modulating the response to statin therapy and therefore influence statin resistance. **2.Lack of effect on the endothelium-dependent vasodilation after targeting LDL-C.** There is much evidence that improvement of endothelium-dependent vasodilation under statin treatment depends on the ADMA levels. At this stage of knowledge, there are two options for the management of this type of statin resistance - the use of a high dose of a statin, or the addition of L-Arginine to the statin. These two strategies are not contradictory, but complementary. **3. The impact of genetic factors on statin resistance.** The resistance to statins has been associated with polymorphisms in the HMG-CoA-R, ABCB1, ABCG2, ABCC1, ABCC2, OATP1B1, OATP2B1, RHOA, NPC1L1, FXR, CYP7A1, ApoE, PCSK9, LDLR, LPA, CETP, and TNF- $\alpha$  genes. However, currently, there is still not enough evidence to advocate pharmacogenetic testing before initiating therapy with statins.

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