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Review

Novel mechanistic and clinical implications concerning the safety of statin discontinuation

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Abstract:
The beneficial effects of statins have been discussed widely, and their preventative role has been confirmed in cardiovascular disorders, primary and secondary prevention settings, and in asymptomatic subjects with a high cardiovascular risk. Despite these benefits, discontinuation of statins is frequent in cardiac patients and might be associated with adverse outcomes in several conditions involving acute coronary syndromes or acute stroke. In this review, we focus on the mechanistic background of statins that might contribute to such negative changes and that extend beyond cholesterol-lowering effects, including the so-called pleiotropic statin activity. In particular, findings regarding the detrimental impact of statin withdrawal on endothelial function, inflammation, platelet activity or AT1 signaling are discussed, along with the possible clinical implications for statin safety.

Key words:
HMG-CoA reductase inhibitors, withdrawal, pleiotropic effects, mechanism

Abbreviations: AMI – acute myocardial infarction, AP-1 – activator protein-1, AT1 – angiotensin II type 1, CAD – coronary artery disease, CK – creatine kinase, CoQ10 – coenzyme Q10, COX-2 – cyclooxygenase 2, CRP – C-reactive protein, eNOS – nitric oxide synthase, FMD – flow-mediated vasodilation, FRAP – ferric reducing ability of plasma, GGPP – geranylgeranylpyrophosphate, GTP – guanosine triphosphate, HMG-CoA – 3-hydroxy-3-methylglutaryl coenzyme A, ICAM-1 – intercellular adhesion molecule –1, IL – interleukin, LFA – leukocyte function-associated antigen 1 receptor, MAPK – mitogen-activated protein kinase, MCP-1 – monocyte chemoattractant protein-1, MMP – matrix metalloproteinase, NADPH – nicotinamide adenine dinucleotide phosphate, NF-κB – nuclear factor κB, NO – nitric oxide, PAI-1 – plasminogen activator inhibitor type-1, PI3K – phosphatidylinositol 3-kinase, PPAR – peroxisome proliferator-activated receptor, ROS – reactive oxygen species, TBARS – thiobarbituric acid reactive substance, TF – tissue factor, TNF-α – tumor necrosis factor-α, tPA – tissue-type plasminogen activator, TXA2 – thromboxane A2, VCAM-1 – vascular cell adhesion molecule-1, VSMC – vascular smooth muscle cell, vWF – von Willebrand factor

Introduction

Withdrawal syndrome involves all the events following an abrupt discontinuation of drug therapy. It is a well-known phenomenon for some cardiovascular drugs; in particular, the withdrawal of β-blockers and nitrates can exert pronounced rebound symptoms, requiring a "stealing out" of the therapy [86]. The results of several studies have suggested that the cessation of statin therapy also might result in a rebound phenomenon.

In recent years, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (HMGRI, statins) have emerged as the most important class of lipid-lowering agents. Several clinical trials have demonstrated and confirmed the beneficial effects of

statins in cardiovascular disorders, in primary and secondary prevention settings, and in asymptomatic subjects with a high cardiovascular risk. Despite these benefits, discontinuation of statins is frequent in cardiac patients [13, 84] and might be associated with adverse outcomes in several conditions, involving acute coronary syndromes or acute stroke [21, 29, 73]. Some authors have suggested that the withdrawal of HMG-CoA reductase inhibitors might lead to worse outcomes than never taking statins [17] and underline that the risk of statin discontinuation seems to be underestimated.

Statin discontinuation rates are quite high, approximately 30% within the first year of prescription [36], and do not seem to be associated with the type of statin administered [29]. Some studies have revealed that up to 40–75% of patients discontinue therapy one year after initiation; unsurprisingly, higher discontinuation rates have been associated with primary CVD prevention, older patients (> 75 years), women, subjects taking concomitant drugs (e.g., cardiovascular drugs, antidepressants or analgesics) and patients with higher medication copayments [57].

The other most common reasons for statin withdrawal are poor efficacy, adverse effects and a lack of conviction regarding the need for treatment [57]. Although HMG-CoA reductase inhibitors are generally well-tolerated drugs, side effects can occur. The serious ones such as elevated liver transaminase levels (defined as > 3 times the upper limit of normal) or elevated creatine kinase (CK) levels (defined as > 10 times the upper limit of normal) linked to myopathy incidences occur in only 0.5% to 2% of clinical trial subjects. Thus, some circumstances merit baseline liver and CK measurements to be taken before and during the period when statin treatment is needed; i.e., in patients over 80 years old, or with liver and muscle disorders, chronic renal insufficiency with diabetes or hypothyroidism, or those who use medications that interact with statins such as fibrates, cyclosporine, warfarin, azole antifungals, macrolides, HIV protease inhibitors, verapamil or amiodarone [77].

In general, the withdrawal of statin therapy might eliminate its protective effect, which in turn would have a detrimental impact on cardiovascular outcomes. In this review, we focus on the mechanistic background that might contribute to such negative changes and that extend beyond the cholesterol-lowering effects, including so-called pleiotropic statin activity (Tab. 1).

Tab. 1. The molecular and clinical aspects of statin discontinuation – a summary

Molecular	
Activation of Rho/Rac proteins	[74]
Decrease of eNOS expression and NO production	[42]
Impairment of flow-mediated vasodilatation	[81]
Increase of vascular superoxide anion generation	[86]
Elevation of proinflammatory interleukins (e.g., IL-6)	[50]
(Re)-elevation of hs-CRP	[89, 90]
Elevation of VCAM-1	[41]
Reduction of plasma tPA and increase of platelet activity	[41, 65]
AT1 up-regulation; increase of AT1 receptors	[8]
Re-elevation of circulating CoQ10 levels	[10]
Clinical	
Increased risk of total mortality in patients after the first acute myocardial infarction	[19]
Increased risk of cardiovascular events, including nonfatal or myocardial infarction and death, in patients with acute coronary syndromes	[29]
Increased risk of mortality during the first year after an acute cerebrovascular event	[13]
Increased risk of early neurologic deterioration, greater infarct volume and death in patients with early ischemic stroke	[5]
Increased risk of subarachnoid hemorrhage	[68]

The pleiotropic effects of statins – a summary

The main physiological background of the cholesterol-independent pleiotropic effects of HMG-CoA reductase inhibitors is the reduction of small guanosine triphosphate (GTP)-binding regulatory proteins resulting from the blockade of farnesyl pyrophosphate production. Protein isoprenylation leads to the covalent attachment, subcellular localization and intracellular trafficking of membrane-associated proteins [85]. G proteins, such as Rho and Rac, are major substrates for post-translational modifications by prenylation [28] and act as molecular switches, transducing a variety of extracellular signals, promoting cell survival, growth and attenuating apoptosis [12, 55].

Some of the beneficial effects mediated by the above mechanisms improve endothelial function. The influence of statins on the endothelium is the most widely described pleiotropic activity of these drugs. The pleiotropic activities involve the up-regulation of endothelial nitric oxide synthase (eNOS) [44], a decrease in vascular smooth muscle cell (VSMC) proliferation and contraction [7, 46], a decrease in macrophage proliferation [2], the reduction of platelet activity [31], the stabilization of atherosclerotic plaque [23] or the reduction of oxidative stress [76] and inflammation [11, 67]. Conversely, the cholesterol-dependent mechanisms by which statins improve vascular function involve the removal of LDL particles, resulting in atherosclerotic-plaque modification, a decrease in vascular inflammation and leukocyte activation [52, 80].

During statin therapy, the reduced activity of isoprenoids induces cytosolic accumulation of non-activated (non-prenylated) Rho/Rac proteins. Statin cessation generates a massive activation of the Rho/Rho-kinase pathway [74], which might, in turn, be the predominant mechanism amplifying the numerous negative changes in endothelial dysfunction, platelet activity or inflammation.

Statin withdrawal and its impact on the endothelium

Nitric oxide (NO)

One of the cholesterol-independent pathways by which statin improves endothelial function is through the up-regulation of endothelial nitric oxide synthase [44, 58]. HMG-CoA reductase inhibitors affect eNOS expression through three pathways: the extension of eNOS mRNA half-life *via* the inhibition of RhoA geranylgeranylation [45]; the reduction of the integral membrane protein caveolin-1, which inhibits nitric oxide (NO) production [64]; or activation of phosphatidylinositol 3-kinase (PI3K)/protein kinase Akt, which phosphorylates and activates eNOS [40]. In addition to the vasodilator activity of endothelial nitric oxide, it modifies inflammatory responses [22], platelet aggregation [37] and smooth muscle cell proliferation [34].

Animal studies have revealed that short-term withdrawal of the statin atorvastatin, given at 10 mg/kg b.w., leads to a profound rebound phenomenon and NO bioavailability impairment [43]. In these studies, it was demonstrated that two days after the withdrawal of statin treatment, endothelial NO production decreased by 90%. Accordingly, statin treatment decreased RhoA membrane expression by 50%, while statin cessation resulted in a 4-fold increase of RhoA in membranes. These effects were not accompanied by elevated serum cholesterol levels, and the molecular mechanism seems rather to involve eNOS up-regulation resulting from the action of the small GTP-binding protein Rho. The authors propose that the increase of Rho isoprenylation negatively regulates eNOS expression. As mentioned earlier, statin administration decreases the synthesis of isoprenoids such as geranylgeranylpyrophosphate (GGPP) *via* the inhibition of mevalonate production, thus inactivating Rho, which cannot be geranylgeranylated and accumulate in the endothelium. The withdrawal of HMGRI restores isoprenoids, increases active Rho protein and decreases NO production.

Additionally, results from animal studies on the detrimental impact of statin discontinuation on endothelial dysfunction with NO impairment implicate another pathway involving the Rac protein. The withdrawal of atorvastatin given to mice at 1–10 mg/kg previously, attenuated NO bioavailability with endothelium-dependent relaxation and increased vascular superoxide anion generation [86]. As the authors discussed, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is activated by Rac, and thus, withdrawal-induced radical generation could be Rac-mediated.

Because NO regulates vascular homeostasis, a decrease in NO production might result in the impairment of vascular function with deregulated vasoconstriction, platelet aggregation, leukocyte adhesion or smooth muscle cell proliferation. As result, cessation of statin therapy might impair vascular homeostasis, thereby enhancing the probability of acute coronary syndromes. These changes could have great importance, especially because NO production may be below baseline levels after stopping the administration of statins [42].

Endothelial dysfunction in ultrasonographic studies

Several studies have revealed that statin cessation might induce endothelial dysfunction. Ultrasonographic assessments demonstrated that the withdrawal of atorvastatin previously given at 80 mg/d (day) to patients with combined hyperlipidemia significantly impaired flow-

mediated vasodilatation (FMD) of the brachial artery. Although FMD in patients treated with statins showed a tendency toward continuous improvement from 4.4% to 6.5% until six weeks, the discontinuation of atorvastatin treatment led to a significant decrease in FMD to below pre-treatment values (4.1%). These changes were particularly apparent in patients with a low baseline FMD. However, this deterioration improved after resuming atorvastatin (20 mg/d) therapy. Changes of FMD in a group with normal baseline values were less pronounced, and this fact might indicate a link between the risk of rebound phenomenon and pre-treatment conditions [81]. Similarly, in another study on patients with coronary artery disease (CAD), the abrupt cessation of simvastatin (20 mg/d) also significantly decreased FMD. The FMD values were lower than the baseline pretreatment levels (4.6% *vs.* 5.6%). These changes were accompanied by a decrease in nitrate production and in eNOS mRNA expression. The FMD level returned to baseline within one week and the nitrate level within 24 h. The authors concluded that abrupt statin discontinuation in patients with CAD might not only negate the beneficial effect of the drug on endothelial function but also impair it further.

Moreover, these negative changes might be more serious in patients with CAD as compared to healthy subjects. Although the decrease of FMD observed on the first day returned to pretreatment status within 1 week in healthy subjects, the same change took longer in patients with CAD. This may suggest that the "rebound effect" after the abrupt cessation of statin treatment could be exaggerated in CAD patients [9].

Inflammatory markers

Inflammation is a key pathophysiological process in the development and progression of atherosclerosis. Several studies show that statins significantly inhibit the inflammatory response mediated by C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), leukocytes, activator protein-1 (AP-1), nuclear factor κB (NF-κB), pro-inflammatory interleukins IL-6, IL-1β, metalloproteinase-9 (MMP-9), monocyte chemoattractant protein-1 (MCP-1) and others. Statins also inhibit the proliferation and migration of vascular smooth muscle cells (VSMC), a process involved in vascular injury, restenosis and atherosclerosis [47]. Recent findings show that statin withdrawal might impact the inflammation state; accordingly, some changes in the levels of inflammatory markers such as CRP, IL or MMP upon therapy discontinuation have been elucidated.

C-reactive protein (CRP)

Acute phase reactant C-reactive protein (CRP) is a nonspecific marker of inflammation and a strong independent predictor of vascular death. CRP has recently emerged as one of the most important mediators directly participating in the pathogenesis of atherosclerosis [79]. Recent studies suggest that CRP is a mediator of atherosclerosis and coronary events by contributing to lesion formation, plaque rapture and coronary thrombosis [53]. Moreover, high-sensitivity (hs)-CRP increases significantly in unstable angina pectoris before coronary stenting. Previous studies emphasize that statin therapy might strongly reduce hs-CRP levels, and this effect is independent of the lipid-lowering activity [89]. Yip et al., in a study of 51 patients with unstable angina pectoris undergoing coronary artery stenting, showed that cessation of statin re-elevated hs-CRP. This effect was prolonged for more than 3 months after atorvastatin (40 mg/d) therapy withdrawal [90]. Similarly, Sposito et al. provided evidence of such changes resulting from stopping statins in a larger prospective cohort study of 249 patients [74]. The withdrawal of statin therapy in patients during acute phase myocardial infarction was linked to an increase in CRP level. The consequence of stopping statin treatment was not only the attenuation of the anti-inflammatory effect but also the development of a pro-inflammatory rebound reaction that might, as the authors suggest, enhance the incidence of recurrent coronary events and systolic dysfunction. In a recent study involving 30 patients with diabetic nephropathy, Rashtchizadeh et al. showed the rapid elevation of hs-CRP levels after three months of lovastatin therapy [66].

The statin-induced CRP-lowering mechanism has not yet been elucidated. The observed effects were independent from lipid profile, which remained unchanged despite ending statin administration [32, 74]. As with the changes in the NO level, the possible explanation of the rebound reaction after statin withdrawal might involve the massive activation of prenylation-dependent proteins such as the small GTPases Rho/Rac [74]. The proposed linkage involves inactivation of Rac-1 proteins, which mediate transcription of CRP in hepatocytes in response to

IL-6 [66]. IL-6 was shown to promote transcription of CRP by means of signal transducer and activator of transcription 3, which in turn is phosphorylated by Rac-1 [49].

The studies performed on the linkage between statin cessation and CRP levels have been characterized by a different duration of analysis, lasting for seven-days to three months after therapy discontinuation. In a study on CAD patients receiving atorvastatin (10 mg/d), short-term drug withdrawal resulted in a rise of CRP levels, which was comparable to statin-naive patients. Furthermore, the short-term administration of statin to these patients caused a decrease in CRP levels. Interestingly, the achieved levels were similar to those seen in patients taking statins for a longer period (two months to two years). The authors concluded that the level of protection achieved by statin is rapid and does not change much during long-term use [83]. Similarly, the cessation of the drug caused an increase in oxidative stress marker levels, which were quantified based on the end products of lipid peroxidation: thiobarbituric acid reactive substance (TBARS) and ferric-reducing ability of plasma (FRAP).

As the recent studies emphasized, C-reactive protein was not the only inflammatory marker determined by the persistence of statin therapy. Another is proinflammatory interleukin-6 (IL-6). In a study on seventeen patients receiving pravastatin (40 mg/d), which was withdrawn after six weeks, IL-6 levels were markedly raised. Despite a positive impact of statins on the inflammatory process, their discontinuation could induce a rebound inflammatory response [50]. As described above, CRP is mostly synthesized by hepatocytes in response to IL-6, which could possibly explain why the abrupt termination of statin therapy might result in a rapid increase of the plasma CRP and IL-6 levels.

von Willebrand factor (vWF)

Re-elevation of hs-CRP might not be accompanied by similar increases in von Willebrand factor (vWF), another factor associated with endothelial damage. In a study analyzing the impact of atorvastatin withdrawal in patients with unstable angina pectoris undergoing coronary artery stenting [90], the concentration of vWF did not differ significantly from the values recorded during statin therapy. This effect was the opposite of the increase in hs-CRP level observed in other studies. The authors hypothesize that endothelial dysfunction or damage does not result from the local inflammatory response. Moreover, increased vWF levels could not be a consequence of plaque rapture, unlike CRP, which mediates such responses. The above theory explaining the differences between CRP and vWF in response to statin withdrawal requires more findings over a longer period of drug discontinuation, perhaps three months.

Vascular cell adhesion molecule (VCAM-1)

Another inflammatory molecule affected by statins is vascular cell adhesion molecule (VCAM-1). VCAM-1 and intercellular adhesion molecule-1 (ICAM-1) belong to the immunoglobulin superfamily of CAMs; VCAM-1 regulates the attachment and transendothelial migration of leukocytes. VCAM-1 expression has been demonstrated to precede macrophage and T-lymphocyte recruitment to atheromatous plaques, and rabbits fed a high-cholesterol diet express VCAM-1 on the endothelium of aortic plaque [1, 4, 19, 48, 70]. The discontinuation of 12-week atorvastatin treatment resulted in a significant elevation of VCAM-1.

Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are several matrix-degrading enzymes, which have been described to be implicated in monocyte/macrophage migration and are diminished by statins [38]. It has been suggested that the activation of MMPs, such as MMP-2, MMP-3, and MMP-9, may facilitate atherosclerosis, plaque destabilization and platelet aggregation resulting in acute coronary events [35, 60]. HMG-CoA reductase inhibitors were shown to lower the expression and function of a broad range of MMPs, including interstitial collagenases (MMP-1, MMP-13), gelatinases (MMP-2, MMP-9) and stromelysin (MMP-3) [2]. Because serum CRP and proinflammatory interleukin IL-6 increase after statin dis-

continuation, similar changes in other inflammatory markers, including metalloproteinases, could be expected. Conversely, in a study on hypercholesterolemic patients receiving simvastatin over at least a six month period, statin withdrawal led to unchanged MMP-2, MMP-9 levels or a reduced MMP-3 level. Interestingly, the observed changes remained over a period of simvastatin (20 mg/d) discontinuation of up to 120 days [30]. The conclusion was that the absence of a rebound in MMP levels might indicate that the inhibitory effects of simvastatin persist over a long period, although the explanation for this is as yet unknown. However, the authors posit the existence of a link between pre-treatment serum MMP levels and the percentage of decline in these serum levels after statin withdrawal. If true, a greater increase in the amplitude of these serum levels could be expected in patients with relatively good inflammatory control, characterized by lower MMP levels before statin withdrawal. In theory, patients with higher metalloproteinase levels do not seem to be at risk of further increase after statin discontinuation. However, further studies on the exact mechanism underlying such changes are required.

Monocyte chemoattractant protein-1 (MCP-1)

Another inflammatory marker, monocyte chemoattractant protein-1 (MCP-1), plays a central role in the development and progression of arteriosclerosis. MCP-1 contributes to the recruitment of monocytes to the vascular wall, and strategies to inhibit MCP-1 attenuate the development of arteriosclerosis in animal models. HMGRIs are known to inhibit the expression of MCP-1, and *in vitro* studies reveal that statin discontinuation might possibly induce MCP-1 expression in VSMCs *via* a non-cholesterol-dependent pathway. This pathway includes small GTPase proteins such as Ras and Rac, which are translocated from the membrane to the cytoplasm as a result of statin administration [6]. Upon statin removal, Rac undergoes a transient "overshoot" translocation back to the membrane, resulting in a rapid increase of the membrane Rac content. Moreover, statin cessation could possibly affect Rac-mediated reactive oxygen species (ROS) generation [24].

Peroxisome proliferator-activated receptor (PPAR)

The peroxisome proliferator-activated receptor (PPAR) is a member of the nuclear steroid-hormone receptor superfamily [33]. The PPARγ isoform is expressed in adipose tissue, smooth muscle, and macrophages and regulates the action of insulin. Peroxisome proliferation is a pleiotropic cellular response to a range of chemical compounds and leads to changes in cellular morphology and enzymatic activity [71]. PPAR isoforms are also activated by fatty acids and fatty acid-derived eicosanoids, or several drugs, including fibrates (PPARα), their structural analogs including antidiabetic agents and thiazolidinediones (PPARγ) [75], and statins. It has been shown that atorvastatin and pravastatin activate PPARγ *via* an increase in PPARγ levels [26, 91]. Additionally, the combined administration of simvastatin and PPARγ agonists resulted in additive effects on atherosclerotic plaque regression [14].

Another anti-inflammatory pathway of statins involves leukocyte function-associated antigen-1 receptors. Statins may bind covalently to lymphocyte function-associated LFA-1 receptors, thereby inhibiting the binding of monocytes and lymphocytes to the adhesion molecules in the artery wall [88]. Until now, no studies analyzing the impact of statin withdrawal on PPAR or LFA-1 regulation have been performed.

Statin withdrawal and its impact on hemostasis

Platelets play a critical role in the manifestation of acute coronary syndromes. Circulating platelets are associated with mural thrombus formation at the site of plaque rupture and vascular injury [51]. In hypercholesterolemia, platelet activity increases and statins decrease their activity through the reduction of serum cholesterol levels and *via* cholesterol-independent pathways. These pathways involve the decrease of platelet activation *via* eNOS up-regulation [42], inhibition of fibrinogen expression and thrombin formation, reduction of platelet aggregation and deposition in diseased vessels, reduction of cyclooxygenase 2 (COX-2) expression, thromboxane A2 (TXA2) and

enhanced synthesis of prostacyclin [16]. Finally, statins affect the fibrinolytic system of vascular smooth muscle and endothelial cells by increasing the expression of tissue-type plasminogen activator (tPA) and inhibiting the expression of plasminogen activator inhibitor type-1 (PAI-1).

The significance of non-sterol mevalonate derivatives on the impact of statins on hemostasis has not been fully established. The processes in which statins seem to be involved are mainly the synthesis of PAI-1, tPA and tissue factor (TF) [39, 72], and these effects are mediated by inhibiting protein prenylation. TF and PAI-1 together or tPA alone are positively associated with the risk of MI and stroke. An elevated PAI-1 level is an independent cardiovascular risk factor associated with atherothrombotic disease, and several studies have shown that statin withdrawal could impair the balance of the fibrinolytic system. Lai et al. described such changes, showing that the positive impact of statin on the increase of tPA and fibrinolysis might end soon after drug discontinuation [41]. They noted a significant reduction of plasma tPA within three days of discontinuation of atorvastatin administration, given at 10 mg/d. In addition, a study on patients with stable coronary heart disease showed a three-fold increase in thrombotic vascular events after simvastatin therapy was stopped, and later when fluvastatin administration was started at lower doses [82]. In a study performed by Puccetti et al., an increase of platelet activity was detected 14 days after cerivastatin withdrawal, and the above changes were accompanied by an increase of oxidized-LDL and decreased platelet NOS activity [65].

The enhancement of prothrombotic activity plays an important role in the pathogenesis of acute vascular events, but the question of whether such changes might negatively impact cardiovascular performance after statin discontinuation is still open to discussion. We already know that, as with other "withdrawal effects", these changes might develop without an elevation in LDL-C cholesterol level [84].

Statin withdrawal and its impact on AT1 signaling

The angiotensin II type 1 (AT1) receptor is known to be implicated in cardiovascular pathophysiology and mediates many biological effects of the renin-angiotensin system, including vasoconstriction, cell growth, water and electrolyte homeostasis, and sympathetic activation [25]. Numerous trials revealed that the AT1 receptor is overexpressed in hypercholesterolemia and a statistically significant correlation between AT1 receptor density and LDL plasma concentration has been demonstrated. It is known that statins downregulate AT1 receptor expression. As *in vitro* and *in vivo* studies show [61, 62, 87], HMGRIs reduced AT1 receptor density, and this effect did not strictly correlate with changes in cholesterol levels. It was emphasized that the mevalonate-GGPP-RhoA pathway might play a pivotal role in statin-induced changes in AT1 receptor activity and in changes resulting from statin discontinuation. The isoprenoid-mediated pathway might promote the preventive role of statin in Ang II-induced cellular and organ damage and in decreases of atherosclerotic lesion or lipid deposition [49]. An *in vitro* study showed that a rapid increase in isoprenoids with increased cytoplasmic levels of unprenylated RhoA after statin withdrawal might explain the AT1 up-regulation [8]. Additionally, the observed effects resulted from a 24-h exposure of VSM cultured cells to simvastatin. The impact of statin withdrawal on AT1 regulation after longer drug exposure requires further study.

Moreover, stimulation of AT1 receptors by Ang II leads to the activation of multiple intracellular signaling pathways, including the activation of mitogen-activated protein kinases (MAPK) in VSMC, resulting in vascular dysfunction. It has been demonstrated that acute withdrawal of statins might result in the activation of MAPK and an increased number of AT1 receptors [8]. The above changes may play a role in the vascular dysfunction caused by statin withdrawal.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a key component of the mitochondrial respiratory chain. It is mainly known for its role in oxidative phosphorylation and its antioxidant properties. The physiological and clinical applications of coenzyme Q10 mainly include exercise performance and anti-fatigue effects as well as the reduction of exercise-induced muscular injury, hypertension, cardiac failure, ischemic heart disease, endothelial function, pre-eclampsia, neurodegenerative diseases and Parkinson's disease [54]. Statins might lead to decreased plasma CoQ10 levels by decreasing

mevalonate synthesis [78]. Moreover, high-dose statins may decrease muscle CoQ10 and mitochondrial respiratory chain activities, which possibly relates to the decrease in the number or volume of muscle mitochondria [63], which in turn might be recognized as an etiological factor of statin-related myopathy.

Additionally, the heart is highly sensitive to CoQ10 deficiency. For example, the reduced energy reserve in heart failure may contribute to the progression of the disease or the development of dilated and hypertrophic cardiomyopathy [56]. Thus, considering the risk of statin-related myopathy or cardiac disease progression, supplementation with coenzyme Q10 has been advocated in situations of pre-existing CoQ10 deficiency, such as in patients with hypercholesterolemia, heart failure and elderly patients who are placed on statin therapy [59]. In a study by Chu et al., the circulating CoQ10 level was rapidly and significantly restored to its pretreatment value on day two after atorvastatin was administered at 10 mg/d to hypercholesterolemic patients [10].

As the authors discuss, farnesyl pyrophosphate is a key intermediary substrate for the enzymes controlling the synthesis of cholesterol, ubiquinone (CoQ10), squalene or isoprenylated proteins, and it was diverted into ubiquinone and dolichol rather than into the cholesterol pathway. This, in turn, could explain why LDL cholesterol levels remained unchanged after atorvastatin withdrawal, unlike CoQ10, which rapidly rebounded to the baseline.

Clinical implications

In the last years there has been growing evidence that acute statin withdrawal can increase coronary and cerebrovascular ischemic patients in patients with vascular risk. According to present knowledge, the clinical consequences of statin withdrawal seem to be especially important in patients with acute coronary syndromes. HMG-CoA reductase inhibitors control important factors involved in the pathology of acute coronary syndromes (i.e., endothelial nitric oxide, endothelin, metalloproteinases, plasminogen activator inhibitor, tissue-type plasminogen activator or free radicals) [29]. Pretreatment with statins reduces cardiac risk in patients with acute coronary syndromes during the first 30 days after onset of symptoms. However, it was demonstrated that the early withdrawal of statin (simvastatin, lovastatin and pravastatin) therapy after the onset of symptoms completely removed this protective effect.

A population-based cohort study of patients who had survived one acute myocardial infarction (AMI) revealed that drug cessation is associated with higher total mortality [19]. A retrospective subgroup analysis of Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) showed that in patients with acute coronary syndromes, stopping the administration of statins might be associated with an increased risk of cardiovascular events, including nonfatal or myocardial infarction and death [29]. The crude rates for myocardial infarction or death at seven days were significantly higher in those who had stopped receiving statins than in patients continuing treatment (8.2 *vs.* 3.8%, $p < 0.05$). Similarly, in another observational study by the National Registry of Myocardial Infarction, the discontinuation of therapy during 24 h of hospitalization due to non-ST elevation myocardial infarction also lead to an increased risk of morbidity and mortality. In-hospital death, chronic heart failure, pulmonary edema, arrhythmia, cardiac arrest and cardiogenic shock were observed more frequently in patients who had withdrawn from statins than in those who continued statin treatment (11.9 *vs.* 5.7%, $p < 0.01$). This was confirmed by the results of another multinational trial by the Global Registry of Acute Coronary Events (GRACE), which revealed that in patients with ST-elevation myocardial infarction, the beneficial effects of statins might be lost rapidly if they are withdrawn during hospitalization. In summary, the discontinuation of statin therapy in unstable patients should be avoided [29].

Moreover, it is not only cardiac patients who seem to be at risk of the negative consequences of stopping statins. Discontinuation might also be detrimental in patients undergoing major non-cardiac surgeries. The dangers include an increased risk of postoperative troponin release, myocardial infarction and death, and could occur in about 25% of patients. The most common reasons behind this risk are a lack of intravenous statin formulation and an inability to take the drug orally shortly after surgery.

Another question is whether such negative consequences could be observed in patients with stable cardiac conditions. The results from a retrospective, large scale Treating New Targets (TNT) trial showed no significant differences in the occurrence of cardiovascular events, assuming the impact of statin discontinuation. However, the lack of randomized trials assessing the issue and the low baseline rate of cardiac events ob-

served in these patients prevent sufficient strength for significant differences to be observed [15].

These studies have been performed on patients with a previous ischemic stroke. Recent reports suggest that statins may have a neuroprotective effect during the acute phase of the stroke *via* a direct influence on the endothelium, inflammatory activity, oxidative stress, platelet function or plaque stabilization. As discussed earlier, statin cessation might in turn have a negative impact on platelet hyperactivity, eNOS expression, NO production, and vascular injury. Animal studies have revealed that such changes might be accompanied by the complete removal of stroke protection by statins as a result of drug cessation. The withdrawal of atorvastatin after a 14-day therapy following focal cerebral ischemia and a 40% statin reduction caused lesion size to reach the control level 4 days after treatment was stopped.

Colivicchi et al. performed a non-randomized study of 631 subjects without clinical evidence of coronary disease but who had been discharged after an acute ischemic stroke. The authors concluded that subjects who discontinue statin therapy of atorvastatin (10–20 mg/d) and simvastatin (20–40 mg/d) might have a significant increase in mortality during the first year after an acute cerebrovascular event [13]. However, others researchers have indicated that these observations should be confirmed in a randomized, double-blinded study [27], especially because results from a SPARCL study showed that here was no impact of statin treatment on stroke recurrence [3]. In another controlled, randomized trial including 215 patients with ischemic stroke [5], statin withdrawal for the first three days after hospital admission due to ischemic stroke caused a significant increase in the risk of early neurologic deterioration, greater infarct volume and death. Considering these reports, some researchers indicate that statin administration should not be interrupted during the acute phase of ischemic stroke.

Additionally, as recent studies have shown, statin withdrawal is associated with an increase in the risk of subarachnoid hemorrhage [68]. This effect might be particularly pronounced in patients who have also stopped antihypertensive drug use. Although the mechanistic background needs further explanation, the detrimental impact of statin discontinuation on the vascular endothelium, which in turn might play a potential role in subarachnoid hemorrhage, could well be a factor. In another study, stopping pravastatin given at 20–40 mg/d in healthy subjects resulted in decreased flow velocity. The authors hypothesize that these effects might be a result of vascular dysfunction due to reduced NO bioavailability and could indicate inappropriate blood supply to active neurons [69].

Studies performed on healthy subjects regarding the possible consequences of statin therapy discontinuation investigated changes in the levels of inflammatory markers, endothelial function or anti-platelet activity. In summary, the results indicate that rapid cessation of statin therapy might lead to the loss of the vascular protective effects and an increase in prothrombotic activity [41].

Additionally, neuromuscular withdrawal symptoms with an elevated creatine kinase level might occur after statin therapy [20]. In a study of fifty-two patients with symptoms of statin-induced myopathy (muscle weakness, myalgia, and CK levels at 1000 U/l) that had persisted for more than three months after statin discontinuation, 10% of the patients had a neuromuscular disorder. These symptoms included an abnormal electromyogram and muscle biopsy, paraneoplastic polymyositis, Kennedy's disease, amytrophic lateral sclerosis, muscle phosphorylase b kinase deficiency, and necrotic myopathy. Because patients with such abnormalities were older and had higher CK levels as compared to patients free of symptoms, the measurement of CK levels seems to be relevant before initiating statin therapy in this group of patients.

Conclusions

The TNT trial showed that in stable CHD, stopping statins for a short time is safe. However, the question is whether it is safe to permanently stop statins or maintain withdrawal for an extended period, especially in acute settings. Some studies indicate that other strategies, such as restarting either at a lower dose or with another, better tolerated statin, should be considered instead [77].

As some studies emphasize, the assessment of the effect of statin withdrawal in high-risk patients will always be limited due to ethical issues [84]. Undoubtedly, if statin therapy is well tolerated, then patient adherence should be monitored by physicians [18]. Additionally, the increasing role of formulations such as

"polypills" and the simultaneous cessation of several drugs such as statins and acetylsalicylic acid have an impact on the safety of therapy.

Considering the differences among statins, such as variations in lipophilicity, which in turn might have consequences on statin pleiotropic activity, there has been no evidence to date suggesting that the negative effects of withdrawal could vary for different HMG-CoA reductase inhibitors. An additional question is whether such effects are dose-dependent, namely if the discontinuation of a statin given at a relatively small dose is not associated with a rapid removal of the protective effects of the drug.

The findings concerning the detrimental impact of drug cessation on the endothelium or hemostasis were characterized over different time periods, lasting from seven days to three months after therapy discontinuation. Moreover, some findings assessing the impact of statin cessation on endothelial function, inflammation or platelet activity are based only on animal studies. Thus, the precise length of time between stopping statin administration and the start of the rebound phenomenon, which results in the levels of several markers returning to similar or higher levels as those seen in statin-naive patients, merits further assessment.

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