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ORIGINAL PAPER

Statins withdrawal, vascular complications, rebound effect and similitude

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Hahnemann considered the secondary action of medicines to be a law of nature and reviewed the conditions under which it occurs. It is closely related to the rebound effects observed with many modern drugs. I review the evidence of the rebound effect of statins that support the similitude principle. In view of their indications in primary and secondary prevention of cardiovascular diseases, statins are widely prescribed. Besides reducing cholesterol biosynthesis, they provide vasculoprotective effects (pleiotropic effects), including improvement of endothelial function, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory and thrombogenic responses, stabilisation of atherosclerotic plaques, and others. Recent studies suggest that suspension of statin treatment leads to a rebound imparing of vascular function, and increasing morbidity and mortality in patients with vascular diseases. Similarly to other classes of modern palliative drugs, this rebound effect is the same as a secondary action or vital reaction described by Samuel Hahnemann, and used in homeopathy in a therapeutic sense. *Homeopathy* (2010) **99**, 255–262.

Keywords: Similitude; Secondary effect; Rebound effect; Paradoxical reaction; Substance withdrawal syndrome; Statin; Vascular diseases; Homeopathy

Samuel Hahnemann considered 'cure by symptom similarity' to be a 'therapeutic law of nature,' stating that after a short-term relief of the enantiopathic, contrary, antipathic, antagonistic, or palliative treatment, aggravation of the original disease follows without exception (*Organon of Medicine*,[1] paragraphs 55–61).

> "*Had physicians been capable of reflecting on the sad results of the antagonistic employment of medicines, they had long since discovered the grand truth, that the true radical healing art must be found in the exact opposite of such an antipathic treatment of the symptoms of disease [...].*" (*Organon*, paragraph 61)

In a physiological explanation of this phenomenon, he says that a 'secondary action or counter-action' occurs automatically after the 'primary action' of every medicine (*Organon*, paragraphs 63–69).

> "*Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed* primary action. *[...] To its action our vital force endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of* secondary action or counter-action." (*Organon*, paragraph 63)

Despite the natural and universal character of this secondary action of the organism, its expression is related to some basic conditions: (1) it appears only in susceptible individuals, who present in their constitution similar symptoms to the pathogenetic effects of the substance; (2) it does not depend on the substance, repetition of the doses or on the type of symptoms (disease); (3) it appears after the primary action of the substance (discontinuation), as an automatic manifestation of the organism; (4) it induces an organic state (symptoms) opposite and greater in intensity and/or duration to the primary action of the substance; (5) its effect magnitude is proportional to the intensity of the primary action (dose) of the substance. (Organon, paragraphs 59, 64, 69).

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The secondary action or vital reaction of the organism is the same as the 'rebound effect' or 'paradoxical reaction' of modern clinical pharmacophysiology, having been described after discontinuation of several classes of currently used drugs ('withdrawal syndrome'), for example, drugs used for the treatment of angina pectoris whose primary effect is the improvement of angina. After suspension of the drug, a rebound effect occurs, consisting of exacerbated thoracic pain, in frequency as well as in intensity. Drugs used to control arterial hypertension can provoke rebound arterial hypertension as a secondary reaction. Anti-arrhythmic medications provoke, after the interruption of treatment, exacerbation of the initial arrhythmias. Anticoagulant drugs whose primary effect is prophylaxis of thrombosis, cause thrombotic complications as a secondary or rebound effect. Bronchodilators cause exacerbation of bronchospasms after the suspension or discontinuation of treatment. In psychiatric medications, central nervous system (CNS) stimulants, antidepressants, anti-psychotics, a reaction of the organism trying to maintain organic homeostasis can be observed, with symptoms opposite to those expected in their primary therapeutic indication have been observed, further aggravating the initial condition. Drugs whose primary action is anti-inflammatory induce a secondary response of the organism, increasing inflammation and the plasma concentration of mediators of inflammation. Drugs whose primary effect is analgesic may provoke, as a paradoxical reaction, hyperalgesia. Diuretics used to decrease blood volume cause rebound retention of sodium and potassium, increasing blood volume. Use of anti-dyspeptics for the treatment of gastritis and gastroduodenal ulcers, cause, after an initial decline in acidity, a rebound increase in acidity.[2–9]

This paper reviews the scientific evidence for undesirable reaction following t the suspension of statins.

Material and methods

Literature was reviewed using the Medline database and the keywords 'statin', 'rebound' and 'withdrawal'. The most relevant papers were selected and the scientific evidence discussed.

Results

Primary action of statins

Statins are the most widely prescribed cholesterol-lowering drugs and are first-line therapeutic agents for the prevention of coronary heart disease and atherosclerosis (the major cause of death in developed countries). Statins act by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in endogenous cholesterol biosynthesis, which catalyses the reduction of HMG-CoA to mevalonic acid. Inhibition of this enzyme has proven to be effective for lowering plasma total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels in humans and can therefore be useful to treat atherosclerotic and dyslipidaemic disorders.

However, the clinical benefits of statins appear to extend beyond their lipid-lowering effects. Besides reducing cholesterol biosynthesis, inhibition of mevalonate by statins also leads to a reduction in the synthesis of important intermediates, such as the isoprenoids (farnesyl pyrophosphate, geranylgeranyl pyrophosphate, coenzyme Q10, dolichol, isopentenyladenosine, etc.). These intermediates are involved in the post-translational prenylation of several proteins (e.g., Ras, Rho and Rac) that modulate a variety of cellular processes including cellular signalling, differentiation and proliferation. Given the central role of these isoprenylated proteins in endothelial function, atherosclerotic plaque stability, platelet activity, coagulation, oxidation and inflammatory and immunologic responses, it could be anticipated that these compounds may exert multiple beneficial primary effects in a broad spectrum of disorders, including cardiovascular disease, osteoporosis, Alzheimer's disease and related vascular dementia, viral and bacterial infection, and others. These cholesterol-lowering-independent effects of statins are termed 'pleiotropic effects', and involving vasculoprotective actions that include improvement of endothelial function, increased nitric oxide (NO) bioavailability, antioxidant properties, inhibition of inflammatory and thrombogenic responses, immunomodulatory actions, regulation of progenitor cells and stabilisation of atherosclerotic plaques.[10–12]

Secondary action or rebound effects of statins

Regardless of the rebound increase in cholesterol biosynthesis, recent scientific evidence suggests that sudden discontinuation of statin treatment leads to rebound impairment of vascular function, and increased morbidity and mortality in patients with vascular diseases. Withdrawal of statins leads to an overshoot activation of heterotrimeric G-proteins Rho and Rac, causing production of reactive oxygen species and reduced NO bioavailability. In humans, discontinuation of statin therapy leads to a pro-oxidant, pro-inflammatory and pro-thrombotic state, with impaired endothelium function. Recent epidemiological studies indicated that cessation of statins in acute myocardial infarction (AMI) and ischaemic stroke patients confers a significantly higher likelihood of early cardiological and neurological deterioration, respectively, and worse outcomes. In summary, withdrawal of statin therapy results in a rapid return to endothelial dysfunction and amplification of the oxidative and inflammatory processes, which may increase cardiac and cerebrovascular risks.[13–16]

Increase of cholesterol biosynthesis

To define the effect of statins on cholesterol biosynthesis in normal subjects, Stone *et al.*[17] investigated the effect of a single oral dose of lovastatin and a 4-week treatment period of lovastatin on mononuclear leucocyte (ML) sterol synthesis as a reflection of total body sterol synthesis. They measured serum lipid profiles and HMG-CoA reductase activity in ML microsomes that had been washed free of lovastatin. The higher dose of lovastatin (40 mg twice

daily.) decreased ML sterol synthesis by $16 \pm 3\%$ ($P < 0.05$) and reduced HMG-CoA reductase activity to 53.7 times ($P < 0.01$) the baseline value at 4 weeks. Stopping this higher dose effected a rebound in ML sterol synthesis to $140 \pm 11\%$ of baseline ($P < 0.01$), while HMG-CoA reductase remained 12.5 times baseline ($P < 0.01$) over the next 3 days. No rebound in serum cholesterol was observed.

To determine whether cessation of statin therapy in human subjects leads to increased cholesterol biosynthesis, Pappu *et al.*[18] measured urinary concentrations of mevalonic acid (an indicator of cholesterol biosynthesis) after the cessation of therapy with lovastatin and simvastatin (80 mg day^{-1}) in patients with heterozygous familial hypercholesterolaemia. Plasma concentrations of LDL-C increased promptly on discontinuation of therapy but did not increase above pretreatment levels at any point after drug discontinuation. Similarly, the 24-h urinary excretion of mevalonic acid was reduced during treatment with lovastatin or simvastatin and increased promptly on discontinuation of drugs.

Chu *et al.*[19] investigated the serial changes of soluble CD40 ligand (sCD40L) and two adipocytokines, adiponectin and resistin, after short-term statin therapy and withdrawal in 32 patients with hypercholesterolaemia who received atorvastatin 10 mg day^{-1} for 3 months. Serum lipid profiles, and levels of sCD40L, adiponectin and resistin, were assessed before and immediately after 3 months' statin therapy. Serum levels of sCD40L and adiponectin were also measured on the 3 consecutive days after statin withdrawal. After 3 months' statin therapy, levels of sCD40L total cholesterol and LDL-C were all reduced significantly ($P < 0.05$). However, sCD40L level tended to increase towards baseline on the first and second days after statin withdrawal, but was not significantly elevated until the third day after withdrawal. Total cholesterol and LDL-C levels did not increase during 3 days of statin withdrawal. No significant changes of adiponectin and resistin levels were seen after statin therapy.

In 30 patients with established coronary artery disease (CAD), Chen *et al.*[20] investigated the effects after withdrawal of simvastatin on serum total cholesterol and LDL-C. After treatment with 20 mg day^{-1} for 4 weeks, abrupt discontinuation of simvastatin leads to a rebound of serum total cholesterol (21.3%) and LDL-C (18.2%) in patients within 1 week, but they were still lower than the baseline values ($P < 0.05$ for each parameter).

Endothelial function

Statins improve endothelial function by up-regulating endothelial NO production that is mediated by inhibiting the isoprenylation of rho GTPase. Withdrawal of statin treatment could suppress endothelial NO production and impair vascular function. To test this hypothesis, normocholesterolaemic mice were treated with atorvastatin (10 mg kg^{-1}) for 14 days, followed by treatment withdrawal: this led to the up-regulation of endothelial NO synthase (eNOS) expression and activity by 2.3- and 3-fold, respectively; withdrawal of statins resulted in a dramatic, 90% decrease of NO production after 2 days. Experimental studies with mouse aortas and cultured endothelial cells clarify the molecular mechanisms that regulate this phenomenon rebound: statins up-regulated the expression of rho GTPase in the cytosol, but statins blocked isoprenoid-dependent rho membrane translocation and GTP-binding activity. Inhibiting the downstream targets of rho showed that rho expression is controlled by a negative feedback mechanism mediated by the actin cytoskeleton. Measuring rho mRNA half-life and nuclear run-on assays demonstrated that statins or disruption of actin stress fibres increased rho gene transcription but not rho mRNA stability. Therefore, treatment with statins leads to the accumulation of non-isoprenylated rho in the cytosol. Withdrawing statin treatment restored the availability of isoprenoids and resulted in a massive membrane translocation and activation of rho, causing down-regulation of endothelial NO production. In summary, the underlying molecular mechanism is a negative feedback regulation of rho gene transcription mediated by the actin cytoskeleton.[21]

In a similar study, 129/SV mice were treated with atorvastatin (10 mg kg^{-1}) for 14 days and then withdrew treatment. Treatment with atorvastatin conferred stroke protection of 40% after filamentous occlusion of the middle cerebral artery followed by reperfusion. Withdrawal of statin treatment, however, resulted in the loss of stroke protection. In mouse aortas and brain vasculature, statins up-regulated eNOS message 2.3- and 1.7-fold, respectively. Withdrawal of statins resulted in 5- and 2.7-fold down-regulation of eNOS mRNA in aorta and brain, respectively, after 2 days. Statin treatment decreased RhoA GTPase membrane expression to 48%, while withdrawal of statins resulted in 4-fold increase of RhoA in the cellular membrane.[22]

To investigate the relationship between simvastatin withdrawal, suppression of endothelial NO production and vascular injury, Chen *et al.*[20] exposed human umbilical vein endothelial cells (HUVECs) to simvastatin. After 24 h, the cells were repeatedly washed to remove the drugs, and the conditioned mediums were collected at the indicated time points. The NO production and levels of eNOS mRNA after 24 h of withdrawal of statins were examined. In HUVECs, a maximum decrease of nitrite levels (−80%) was observed at 6 h after stopping simvastatin treatment, which was below the control levels. Twenty-four hours after stopping 10^{-5} and 10^{-6} mmol l^{-1} simvastatin treatment, eNOS mRNA expression decreased to −71% and −42% ($P < 0.05$), respectively. The authors concluded that vascular injury may be related to the suppression of endothelial NO production, which is dose-dependent, and independent of cholesterol levels.

The effect of initiation and withdrawal of statin therapy on resting and functionally activated cerebral haemodynamics was investigated in healthy young volunteers: 60 normocholesterolaemic students were subjected to a placebo-controlled, double-blind crossover study with a washout phase between blocks of 4 weeks; in the verum group, 20 mg pravastatin was taken for 2 weeks followed by 40 mg for 4 weeks. As the main outcome, resting and evoked haemodynamic responses due to a visual

stimulation task in the posterior cerebral artery were obtained at baseline and then weekly and the day after discontinuation. The day after statin withdrawal evoked flow velocity responses were significantly lower ($11 \pm 4\%$ *vs.* $13 \pm 5\%$ at baseline, $P < 0.01$), indicating inappropriate blood supply of active neurons. This reduction in evoked flow velocity responses reflects reduced NO bioavailability and therefore supports molecular findings of acute statin withdrawal.[23]

Increase of inflammation and oxidative stress

In addition to its lipid-lowering properties, statin decreases the level of C-reactive protein (CRP) that is considered a risk factor for CAD. Withdrawal of statin therapy, stimulating the growth rebound in the level of CRP, could increase the incidence of cardiac events in patients with atherosclerotic heart disease. To test this hypothesis, 20 patients with hyperlipidaemia received statin (atorvastatin, 10 mg day^{-1}) therapy for 3 months. The levels of lipid profiles and CRP were assessed before receiving the statin therapy, immediately after 3 months of therapy and on the 3 consecutive days after withdrawal of statin treatment. After 3 months of statin therapy, the total cholesterol, LDL-C and CRP were significantly reduced. The level of CRP increased on the second day after withdrawal of statin therapy (2590.14 ± 1045.05 *vs.* 1257.95 ± 207.99 ng ml^{-1}); however, the total cholesterol and LDL-C did not increase during the 3-day period after withdrawal of statin therapy.[24]

Li *et al.*[25] investigated whether acute termination of statin treatment could result in rebound of inflammatory markers, such as CRP and interleukin-6 (IL-6), in patients with hyperlipidaemia. Seventeen patients with hyperlipidaemia were given 40 mg day^{-1} of pravastatin for 6 weeks. The concentrations of plasma CRP and IL-6 were evaluated before receiving the statin therapy, immediately after 6 weeks of pravastatin therapy and at days 1, 3 and 7 after withdrawal. The lipid profile was also evaluated at baseline, 6 weeks of therapy and at day 7 after terminating pravastatin. Pravastatin therapy induced significant reductions in total cholesterol. Although the lipid profile did not change during the 7-day period after withdrawal of pravastatin therapy, the concentrations of CRP and IL-6 increased significantly. No correlation between increase of CRP as well as IL-6 and small changes of LDL-C concentrations was found after withdrawal of pravastatin therapy at day 7.

To assess whether variations in antioxidant and anti-inflammatory parameters occur with short-term administration and discontinuation of atorvastatin in normocholesterolaemic CAD patients, 40 CAD patients with near-normal serum cholesterol levels (total cholesterol < 240 mg dl^{-1}, LDL-C < 130 mg dl^{-1}) were continuously randomised to groups A and B (20 patients taking atorvastatin) and groups C and D (20 patients not taking atorvastatin). Atorvastatin (10 mg day^{-1}) was continued in group A, withdrawn in group B and started in groups C and D for 6 weeks. Thereafter, atorvastatin was withdrawn in groups A and C, restarted in group B and continued in group D for further 6 weeks. CRP and markers of oxidative stress were assessed at baseline, 6 weeks and 12 weeks in all the groups. The results showed that administration and withdrawal of atorvastatin caused changes in markers of oxidative stress, which closely correlated with changes in marker of inflammation.[26]

In a prospective observational cohort study, Sposito *et al.*[27] verified the existence of a rebound inflammatory effect after statin withdrawal in the acute phase of myocardial infarction (MI): changes in CRP between the first and the fifth day after MI were evaluated in 249 consecutive patients who were using statins prior to and during MI (SS), statins prior to but not during MI (SN), no statin prior to but during MI (NS) and no statin prior to nor during MI (NN). At baseline, statin users presented a trend to lower median CRP values as compared with those without this treatment before the MI. By the fifth day, median CRP was significantly higher in the SN group than in the other groups ($P < 0.0001$). At the fifth day, the median CRP in the NN group was lower than in the SN group ($P < 0.0001$), but higher than in the NS and SS groups ($P < 0.0001$). There was no significant correlation between CRP change and the change of LDL-C, high-density lipid (HDL)-cholesterol or triglycerides. The present study has provided evidence for the existence of an important rebound inflammatory effect after statin cessation.

Stimulation of thrombogenic response

The use of statins is associated with a primary reduced thrombosis burden and diminished platelet activity reducing cardiovascular events. To test platelet activity rebound after statin withdrawal, Puccetti *et al.*[28] evaluated platelet activity after cerivastatin discontinuation in 18 subjects and in 16 subjects continuing treatment with simvastatin, measuring LDL-C, oxidised-LDL (ox-LDL) platelet P-selectin (P-sel) expression, platelet aggregation and intracellular citrullin production (iCit) as an indicator of intracellular NO synthase activity, at baseline and 7, 14, 28 and 60 days after statin discontinuation. P-sel expression and platelet aggregation were increased at 14 days ($P < 0.001$ and $P < 0.05$, respectively) in association with raised ox-LDL ($r = 0.30$, $P < 0.05$) and decreased iCit ($r = 0.53$, $P < 0.01$). Increased LDL-C was related to P-sel and platelet aggregation at 28 days ($r = 0.30$, $P < 0.05$). Subjects continuing statin treatment had no significant changes of P-sel at 28 ($P = 0.221$) and 60 days ($P = 0.238$).

Observational studies

Heeschen *et al.*[29] investigated the effects of statins on the cardiac event rate in 1616 patients of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM), study who had CAD and chest pain in the previous 24 h, recording death and non-fatal MI during the 30-day follow-up. Baseline clinical characteristics did not differ among 1249 patients without statin therapy, 379 patients with continued statin therapy and 86 patients with discontinued statin therapy after hospitalisation. While statin therapy was associated with a reduced event rate at 30-day follow-up compared with patients without statins (adjusted hazard ratio 0.49, 95% CI 0.21–0.86, $P = 0.004$), if the statin

therapy was withdrawn after admission, cardiac risk increased compared with patients who continued to receive statins (2.93, 95% CI 1.64–6.27, $P = 0.005$) and tended to be higher compared with patients who never received statins (1.69, 95% CI 0.92–3.56, $P = 0.15$). This was related to an increased event rate during the first week after onset of symptoms and was independent of cholesterol levels. Similarly as in subsequent re-assessment of the data,[30] the authors concluded that discontinuation of statins after onset of symptoms completely abrogates the primary beneficial effect.

An observational study compared 13,871 patients with acute coronary syndrome (non-ST-segment-elevation MI) previously receiving statins before hospital admission (9001 patients continued receiving statins within 24 h of hospital admission and 4870 patients discontinued therapy) with 54,635 patients who did not receive statins at any time before or during hospitalisation, enrolled in the National Registry of Myocardial Infarction 4. Patients who discontinued treatment had increased hospital morbidity and mortality rates relative to patients in whom therapy was continued, with higher rates of heart failure, ventricular arrhythmias, shock and death. In multivariate analyses, these patients were at statistically significant increased risk of hospital death compared with those continuing statin therapy and at similar risk compared with those not receiving statins before or during hospitalisation.[31]

Using the same database, Fonarow *et al.*[32] analysed in-hospital morbidity and mortality comparing patients who continued statin therapy received before the index AMI hospitalisation ($n = 17\,118$) or newly started statin therapy within the first 24 h of hospitalisation ($n = 21,978$) and patients who did not receive early statin treatment ($n = 126,128$) or whose statin therapy was discontinued ($n = 9411$). While new or continued treatment with a statin in the first 24 h was associated with a decreased risk of mortality compared with no statin use (4.0% and 5.3%, respectively, compared with 15.4% no statin), discontinuation of statin treatment was associated with a slightly increased risk of mortality (16.5%). Propensity analysis yielded mortality odds ratios of 0.46 for continued therapy, 0.42 for newly started therapy and 1.25 for discontinued therapy for matched pairs *vs.* no statin therapy (all P values < 0.0001).

Aiming to assess the effect of perioperative statin withdrawal on postoperative cardiac outcome, Schouten *et al.*[33] studied 298 consecutive statin users who underwent major vascular surgery on days 1, 3, 7 and 30 postoperatively. End points were postoperative troponin release, MI and a combination of non-fatal MI and cardiovascular death. Statin discontinuation was associated with an increased risk for postoperative troponin release (hazard ratio 4.6, 95% CI 2.2–9.6) and the combination of MI and cardiovascular death (hazard ratio 7.5, 95% CI 2.8–20.1). In conclusion, the present study showed that statin withdrawal in the perioperative period is associated with an increased risk for perioperative adverse cardiac events.

Retrospective analyses of data from the PRISM, the National Registry of Myocardial Infarction 4 and the Global Registry of Acute Coronary Events (GRACE) trials revealed that the benefits of statins on acute coronary outcomes are rapidly lost and outcomes worsened if statins are discontinued during a patient's hospitalisation for an acute coronary syndrome. Withdrawal of statin therapy in the first 24 h of hospitalisation for non-ST-elevation MI increased the hospital morbidity and mortality rate *vs.* continued therapy (11.9% *vs.* 5.7%, $P < 0.01$). In patients with acute coronary syndromes who discontinue statins, the rapid increase in risk of an event may result not only from the lost benefits from the therapy, but also from rebound inhibition of vascular protective substances and activation of vascular deleterious substances. The authors concluded that acute removal of pleiotropic effects and rebound vascular dysfunction may be more important in an acute coronary event, where inflammation promotes rupture of atherosclerotic plaques and inflammatory and prothrombosis markers are present in high concentration, than in stable chronic vascular disease.[34]

Vascular endothelium, which can be affected by statins, is believed to play a substantial role in subarachnoid haemorrhage (SAH). In order to estimate the association between use and withdrawal of statins and the risk of SAH, Risselada *et al.*[35] conducted a population-based case–control study within the PHARMO database: a case was defined as a person hospitalised for SAH in the period 1998–2006, and 10 randomly chosen controls were matched to each case on age, gender and calendar date. During the study period, 1004 incident cases of SAH were identified, and current use of statins did not significantly decrease the risk of SAH (OR 0.77, 95% CI 0.55–1.07). The odds ratio for recent withdrawal compared to non-users was 1.62 (95% CI 0.96–2.73). Compared to current use, recent withdrawal was associated with an increased risk of SAH (OR 2.34, 95% CI 1.35–4.05). Interaction analysis showed that the effect of statin withdrawal was highest in patients who had also recently stopped antihypertensive drugs (OR 6.77, 95% CI 2.10–21.8). The authors concluded that statin withdrawal increased the risk of SAH by a factor 2, even more in patients who had also recently stopped their antihypertensive treatment.

Interventional studies

In a retrospective analysis of the relationship between compliance and treatment effect in 1677 patients (after a successful first percutaneous coronary intervention) enrolled in LIPS (Lescol Intervention Prevention Study: 844 in the fluvastatin group and 833 in the placebo group), Lesaffre *et al.*[36] showed that discontinuing fluvastatin without switching to another lipid-lowering medication increased the risk of major adverse cardiac events (MACE) compared with that of patients who stayed on fluvastatin (relative risk (RR) 2.27, 95% CI 1.60–3.23, $P < 0.001$) and the increase in the risk of MACE was greater than that associated with discontinuing placebo ($P = 0.032$).

Aiming to assess the impact of discontinued statin therapy on clinical outcome in patients discharged after an acute ischaemic stroke, Colivicchi *et al.*[37] followed 631 consecutive stroke survivors for 12 months without clinical

evidence of coronary heart disease. Within 12 months from discharge, 246 patients (38.9%) discontinued statin therapy; the mean time from discharge to statin discontinuation was 48.6 ± 54.9 days (median time 30 days, interquartile range 18–55 days). During follow-up, 116 patients died (1-year probability of death 0.18, 95% CI 0.15–0.21). Multivariate analysis demonstrated that after adjustment for all confounders and interactions, statin therapy discontinuation (hazard ratio 2.78, 95% CI 1.96–3.72, $P = 0.003$) was an independent predictor of all-cause 1-year mortality. The authors concluded that a large number of patients discontinue their use of statins early after acute stroke. Moreover, patients discontinuing statins have a significantly increased mortality during the first year after the acute cerebrovascular event.

In a controlled randomised study, Blanco *et al.*[38] investigated the influence of statin pretreatment and its withdrawal on the outcome of acute ischaemic stroke patients: from 215 patients admitted within 24 h of a hemispheric ischaemic stroke, 89 patients on chronic statin treatment were randomly assigned either to statin withdrawal for the first 3 days after admission ($n = 46$) or to immediately receive atorvastatin 20 mg day^{-1} ($n = 43$). The primary outcome event was death or dependency (modified Rankin Scale (mRS) score > 2) at 3 months. Early neurologic deterioration (END) and infarct volume at days 4–7 were secondary outcome variables. In a secondary analysis, outcome variables were compared with the non-randomised patients without previous statin therapy ($n = 126$). Patients with statin withdrawal showed a higher frequency of mRS score > 2 at the end of follow-up (60.0% *vs.* 39.0%, $P = 0.043$), END (65.2% *vs.* 20.9%, $P < 0.0001$) and greater infarct volume (74 *vs.* 26 ml, $P = 0.002$) compared with the non-statin-withdrawal group. Statin withdrawal was associated with a 4.66-fold increase in the risk of death or dependency, an 8.67-fold increase in the risk of END and an increase in mean infarct volume of 37.63 ml (standard error (SE) 10.01, $P < 0.001$) after adjusting for age and baseline stroke severity. Compared with patients without previous treatment with statins, statin withdrawal was associated with a 19-fold increase in the risk of END and an increase in mean infarct volume of 43.51 ml (SE 21.91; $P = 0.048$). The authors concluded that statin withdrawal is associated with increased risk of death or dependency at 90 days.

Chen *et al.*[20] investigated the effects after withdrawal of simvastatin on brachial artery endothelial function in 30 patients with established CAD compared to 20 healthy subjects as control group. Endothelial-dependent flow-mediated vasodilation (FMD) was assessed in the brachial artery using high-resolution ultrasound at baseline, 4 weeks during simvastatin treatment and 1 week after termination of therapy. A significant decreased of FMD (−59.3%) was observed in patients after discontinuation of simvastatin in 1 week, and furthermore, the FMD was even lower than the baseline levels (4.6% *vs.* 5.6%, $P < 0.05$). In healthy subjects, abrupt discontinuation of therapy caused a rapid and significant decrease in FMD from 10.6% to 5.2% at day 1, but it returned to baseline levels within 1 week.

Discussion

Despite the numerous studies that demonstrate the primary vasculoprotective action of statins (pleiotropic effects), recent scientific evidence suggests that discontinuation of treatment results in a rapid (<7 days) return to endothelial dysfunction and amplification of the oxidative and inflammatory processes (rebound effects), increasing morbidity and mortality in patients with coronary artery and cerebrovascular diseases.

Experimental studies have described the physiological and molecular mechanisms involved in 'statin withdrawal syndrome', expanding the knowledge of the spectrum of action of this 'vital reaction':

1) *increase of markers of cholesterol biosynthesis*: decrease of 12.5-fold in HMG-CoA reductase,[17] and increase in ML synthesis baseline (1.4-fold),[7] ox-LDL,[28] LDL-C[18,20,28] (18–30%), urinary concentrations of mevalonic acid[18] and sCD40L.[19]
2) *worsening of endothelial function*: in mice, decrease in NO production (90%),[21] down-regulation of eNOS in aorta and brain (2.7- to 5-fold)[22] and increase of RhoA GTPase in cellular membrane (4-fold).[22] In human, decrease in NO production (decrease of 90% in eNOS mRNA expression in HUVEC)[20] and intracellular iCit production.[28]
3) *increase of inflammation and oxidative stress*: increase in the level of C-reactive protein (0.8- to 2.5-fold),[24–27] in IL-6[25] and in markers of oxidative stress (phenolic antioxidants FRAP and TBARS).[26]
4) *stimulation of thrombogenic response*: increase in P-sel expression and platelet aggregation.[28]

Plasma concentrations of cholesterol did not increase above pretreatment levels after statin discontinuation,[18–20] probably because the observation period was short (<7 days).

In a general analysis, the cited observational studies[30–35] showed that statins withdrawal resulted in an increased risk of mortality (secondary to fatal vascular events) when compared with the maintenance (2.3- to 7.5-fold) and the absence (1.25- to 1.69-fold) of treatment. The interventional studies showed that the suspension of statins led to a significantly increased risk of mortality in relation to maintenance treatment (4.66-fold),[38] and a significantly increased risk of fatal vascular events regarding the maintenance of treatment (2.27- to 8.67-fold),[36,38] the absence of treatment (19-fold)[38] and placebo.[36] Statin discontinuation was an independent predictor of all-cause 1-year mortality.[37]

Statins are now very widely used. In 2002, a Pfizer Laboratory survey estimated that 44 million people worldwide were taking atorvastatin, and the total exceeded 100 million when other statins were included (simvastatin, pravastatin, lovastatin and fluvastatin).[39] By 2007, this had increased to an estimated 145 million users of atorvastatin, and 250 million people taking all statins.[40]

Continuous and prolonged use of statins (>1 year) is required to achieve the vasculoprotective effects, but studies

have showed that approximately 50% of patients discontinued medication within 6 months of starting therapy,[41,42] predisposing, according to estimates cited, 125 million of users to the occurrence of automatic secondary action of the organism.

This withdrawal syndrome affects a small portion of the population (<5%), but may affect 125–625 thousand people if prevalence is similar to the 0.1–0.5%, described for long-acting β agonists (LABA) and SSRIs, respectively.[6–9]

The recent recommendation of indiscriminate use of statins in primary and secondary prevention of vascular events, including healthy individuals,[43,44] might make this undesirable paradoxical reaction a problem with great impact on public health if users are not warned about the risks of abrupt discontinuation of treatment.[45]

Again, modern scientific evidence confirms Hahnemann's postulates and the principle of similitude employed in homeopathic treatment.

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