Till death us do part?

Postoperative statin discontinuation

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Introduction

With increasing frequency, anaesthesiologists are being presented with patients on chronic statin therapy or themselves prescribing statins to patients perioperatively. The reasons are twofold. Firstly, statin therapy is widely used for primary and secondary prevention of cardiovascular complications of atherosclerosis. Secondly, recent studies (supported by meta-analyses) provide relatively strong evidence that statins cost-effectively reduce the risk of myocardial infarction through both non-cardiac and cardiac surgery. The available meta-analyses suggest that the risk reduction gained from perioperative statin therapy is clinically significant. Hindler and colleagues' meta-analysis indicated that statin therapy was associated with 38% and 59% reductions in cardiac mortality after cardiac and vascular surgery respectively. Kapoor and colleagues' estimated that statin users had a 30 to 42% lower postoperative incidence of cardiac death or acute coronary syndrome compared with patients in which no statin therapy was administered perioperatively.

Pathophysiology of perioperative myocardial infarction

Atherosclerotic lesions cause perioperative myocardial infarction predominantly via two pathophysiological mechanisms. Firstly, approximately half of all perioperative myocardial infarctions are secondary to prolonged stress-induced ischaemia in the presence of high-grade coronary stenoses. The peak incidence of myocardial infarction associated with this mechanism occurs on the second postoperative day. The perioperative administration of beta-adrenergic blockers, titrated to achieve tight heart-rate control in high-risk patients, is useful in limiting stress-induced ischaemia associated with high-grade coronary lesions.

The second mechanism responsible for perioperative myocardial infarction is rupture or fissuring of the fibrous cap of an atherosclerotic plaque, or endothelial cell desquamation. Mature atherosclerotic plaques consist predominantly of two components: an area of soft, lipid-rich, necrotic cellular material (atheroma) which is encapsulated by fibrous acellular collagen-rich connective tissue (sclerosis), the latter structure being termed the fibrous cap. Fibrous-cap rupture and endothelial cell desquamation expose blood to thrombogenic substances and surfaces which can ultimately lead to coronary thrombosis. The factors making atherosclerotic lesions vulnerable to rupture include a large necrotic lipid core comprising more than 40% of the total volume of the plaque and a thin fibrous cap less than 65 to 150 microns thick. These characteristics confer a high wall tension to the fibrous cap and atherosclerotic plaques have indeed been described to rupture at the point of maximal tension.

Poldermans and Schouten hypothesise that the postoperative inflammatory response involving release of pro-inflammatory cytokines such as tumour necrosis factor alpha, interleukin-1 and interleukin-6, can make atherosclerotic plaques more vulnerable to rupture because of thinning of the fibrous cap (with consequent reduction in strength and increased wall tension). The transformation from a stable atherosclerotic lesion to vulnerable plaque can take place postoperatively in a relatively short period of time. Myocardial infarction caused by plaque rupture can occur at any time postoperatively.

An improved understanding of the pathophysiology of perioperative myocardial infarction has led to new approaches to the problem. Libby succinctly summarised the previous approach: “The greater the stenosis, the greater the risk of a clinical event”. In other words, both cardiologists and anaesthesiologists tended to focus on the identification of high-grade coronary stenoses and whether they represented a problem that needed to be addressed before non-cardiac surgery. Two evolutionary concepts currently challenge this approach. Firstly, unless indicated medically, prophylactic attempts to bypass stenotic lesions have had doubtful success in reducing postoperative infarction and mortality. Secondly, the emphasis nowadays has shifted from the focus on identification of high-grade lesions to identification of patients likely to have vulnerable (inflamed) atherosclerotic plaque. (A valid alternative perspective suggests that the severity of coronary stenoses are indicators of plaque load, i.e. “they serve as a marker for the presence of angiographically modest or even unapparent atherosclerotic plaques actually more prone to rupture.”) The utility of perioperative statin therapy is that it improves the stability of vulnerable plaques, reducing their risk of rupture and thus incidence of perioperative myocardial infarction and other myocardial ischaemia-related complications.

Considering the pathophysiology of the two archetypal types of lesions causing perioperative myocardial infarction, we could hypothesise that a combination of beta-adrenergic blockers and statins will act synergistically to reduce postoperative cardiac complications. The study conducted by Kertai and colleagues addressing this question was unfortunately underpowered to
detect a difference in postoperative cardiac complications. However, this hypothesis is currently being tested in the Decrease IV study.6,7

A brief overview of the mechanisms of action of statins

For a more exhaustive description of the mechanisms whereby statins reduce or peripherally. (peripheral) complications of atherosclerotic lesions, the interested reader is referred to other reviews of the topic.84,85 Statins are a group of drugs that have in common the ability to inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase,7 the enzyme that catalyses the conversion of HMG-CoA to mevalonate in hepatic and other tissues. The conversion of HMG-CoA to mevalonate represents the rate-limiting step in the hepatic synthesis of LDL-cholesterol.46,69,71 Statin therapy can induce a 50 to 60% reduction in LDL-cholesterol levels within four weeks of initiating treatment.8 A 10% reduction in LDL-cholesterol has been linked to an approximately 10% reduction in coronary events,8 while statin-induced lowering of LDL-cholesterol reverses this deleterious effect.8,72

1. Endothelial nitric oxide synthetase (eNOS) is predominantly found in caveolae, and its function is inhibited by binding to caveolin-1, a protein found in caveolae. Hyperlipidaemia increases caveolin-1, thereby inhibiting nitric oxide production, while statin-induced lowering of LDL-cholesterol reverses this deleterious effect.9,72

2. Reduction in LDL-cholesterol results in anti-inflammatory effects. a. Nitric oxide’s ability to reverse endothelial cell overexpression of adhesion molecules confers on it atheroprotective and anti-inflammatory properties in addition to its vasodilatory characteristics.8,71

b. Lymphocytes’ ability to respond to exogenous signals is synchronised by proteins that collect in LDL-cholesterol-rich areas of the cell membrane called lipid rafts.4 The function of lipid rafts is to bring together molecules essential for the activation of the immune cells, but also to separate these molecules when the conditions for activation are not appropriate. There is evidence that statin-induced decreases of LDL-cholesterol disrupts lipid rafts, thereby limiting the cellular immune response, an important determinant of atherogenesis.1

3. Reduction in LDL-cholesterol levels limits inflammation and apoptosis of macrophage foam cells in atherosclerotic lesions. The reduction in necrotic lipid core volume decreases wall tension, making plaques less vulnerable to rupture.86,91 The word “pleiotropic” (derived from two Greek words, “pleion” and “tropos”, meaning “many turns”), was originally used in genetics to describe the ability of a single gene to affect multiple phenotypic effects in an organism.76

While the benefits of statin therapy were originally linked to the degree of reduction in LDL-cholesterol,12,45 more recent studies suggest that many beneficial effects of statins occur within hours of administration and weeks before LDL-cholesterol levels decrease.14,90 The non-LDL-cholesterol-related “pleiotropic effects”90-92 of statins are predominantly secondary to their inhibition of isoprene pathway functioning. Statin-induced HMG-CoA reductase inhibition hampers isoprene pathway functioning because inadequate amounts of farnesyl and geranylgeranyl pyrophosphate are available to add isoprene chains (termed isoprenylation) to the small G-proteins (also called GTAPases), Rho, Ras and Rac.93 These isoprenes chains serve as lipid attachments that allow these GTAPases to attach to the inside of the cell membrane. The membrane-bound GTAPases act as molecular switches and co-ordinate the activation of a wide range of intracellular processes.93 Isoprene pathway inhibition has the following beneficial effects in atherosclerosis:

1. Inhibition of isoprenylation by statins halves the amount of membrane-bound Rho GTAPase.93 This stabilises eNOS mRNA, increasing its half-life from 13 to 38 hours; the consequence is a threefold greater production of nitric oxide.6,95-98

2. Isoprenylated membrane-bound Rho GTAPase activates nuclear factor kappa beta (NFkB) in endothelium, platelets and leucocytes.78 Activated NFkB promotes inflammation by promoting endothelial cell and leucocyte expression of adhesion molecules and nuclear transcription of pro-inflammatory cytokines.94 This is associated with a decrease in heparinically generated acute-phase proteins, particularly pro-inflammatory and pro-atherosclerotic C-reactive protein (CRP).95,103-105 Statin-induced inhibition of isoprene pathway functioning limits the deleterious pro-inflammatory consequences.

3. Reduced endothelial inflammation and expression of adhesion molecules after statin administration both diminishes leukocyte-endothelial interaction106 and limits subsequent leukocyte trafficking. Reduced numbers of intimal mononuclear cells disperse the macrophage foam cell17,78,106 expression of matrix metalloproteinases71,75,109,110, while at the same time allowing proliferation and better functioning of smooth-muscle cells.71,103 Both of these mechanisms enhance collagen synthesis35 and inhibit neointimal deposition.

4. In atherosclerosis, inflammatory mediators cause macrophages, smooth-muscle and endothelial cells to over-express tissue factor92,112 and the ratio of plasminogen activator inhibitor-1 to tissue plasminogen activator increases. Both factor clot development should plaque rupture occur. Statin-induced isoprene pathway inhibition and anti-inflammatory effects reverse these potentially deleterious processes.71,106,112,113 Greater expression of nitric oxide also inhibits platelet aggregation, an effect that is accentuated by the lowering of LDL-cholesterol.71,74,114

It is interesting that the statin-induced decrease in LDL-cholesterol and isoprene pathway inhibition both result in similar effects, albeit via disparate mechanisms. These effects can be summarised as follows:

1. Enhanced endothelial function, actioned by improved expression of nitric oxide and reduced expression of adhesion molecules with limited trafficking of macrophages.

2. The promotion of anti-inflammatory and anti-atherosclerotic endothrocyte trafficking, an effect that enhances plaque stability.

3. The facilitation of physiological anticoagulant and fibrinolytic responses.

The relative importance of LDL-cholesterol lowering versus the pleiotropic effects of statins has been a matter of debate. What is clear at this time is that reduction in LDL-cholesterol represents a late benefit to the patient, while the pleiotropic effects represent an early benefit.

Consequences of postoperative statin discontinuation

Two studies investigating the effects of postoperative statin discontinuation on cardiac outcome after vascular surgery were published in 2007. In the most recent study, Schouten and colleagues115 observed that postoperative statin discontinuation resulted in increased troponin release (hazard ratio 4.6, 95% confidence interval 2.2 to 9.6) as well as an increase in the combined outcome of myocardial infarction and cardiovascular death (hazard ratio 7.5, 95% confidence interval 2.8 to 20.1). An important observation made in this study was that preoperative administration of a slow-release fluvastatin preparation was associated with fewer postoperative cardiac events compared with the use of standard atorvastatin, simvastatin or pravastatin preparations.

In the other 2007 study, Le Manach and colleagues116 interrogated a comprehensive database of vascular-surgery patients for postoperative “cardiac myonecrosis”, which they defined as an increase in troponin I serum concentrations exceeding 0.1 ng/ml, a value that exceeds the 99th percentile for troponin I serum levels. These investigators observed that failure to re-institute statin therapy by the fourth postoperative day was a significant predictor of postoperative cardiac myonecrosis (odds ratio: 2.9, 95% CI 1.6 to 5.5).

Acute benefit after early initiation of statin therapy in acute coronary syndromes

The conclusions of the abovementioned anaesthesia-related
studies are in agreement with the available evidence that statin discontinuation has deleterious effects on short-term outcome after presentation with an acute coronary syndrome (ACS). It is also relevant that early initiation of statin therapy appears beneficial after presentation with an ACS.

Patients presenting with an ACS are known to have a significant risk of a future recurrent event, because of the prevalence of other vulnerable plaques that are as prone to rupture as the culprit lesion. The statins’ powerful anti-inflammatory effects will stabilise vulnerable plaques and presumably reduce this risk. The GRACE (Global Registry of Acute Coronary Events) study enrolled 19,537 patients admitted to 94 hospitals in 14 countries that presented with an ACS. Patients not previously taking statins who began statin therapy while still in hospital were less likely to die than patients who never received statin therapy. This represented the first investigation indicating that early initiation of statin therapy in patients with ACS resulted in fewer hospital complications. The subsequent MIARCIL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) and PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22) study121,122 both confirmed the findings of the GRACE study. They indicated that early initiation of intensive statin therapy (within 24 to 96 hours) after presentation with ACS resulted in a reduction of up to 25% in the incidence of subsequent cardiovascular events and death. It confirmed the findings of the MIARCIL study that incorporated data from more than 300,000 patients. They too, concluded that both continued and new statin therapy initiated within 24 hours of admission were associated with a significantly lower odds ratio of developing complications than if no statin at all was administered.

Two meta-analyses123,124 have been published on the efficacy of statin therapy in ACS. The first123 confirms the benefits (particularly reductions in cardiovascular death, unstable angina and need for revascularisation) of initiating ACS. The two meta-analyses suggested as possible in acute coronary syndromes, while the second124 could only verify a reduction in unstable angina four months after initiation of therapy.

Acute loss of benefit following statin withdrawal after acute coronary syndromes

Early discontinuation of statin treatment resulting in the acute loss of its protective benefit in ACS was initially described in a subgroup analysis of the PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management) database.124,125 Although the authors themselves criticised this study as being statistically flawed, subsequent analysis confirmed that discontinuation of statins was indeed associated with an almost threefold higher mortality and non-fatal myocardial infarction rate, than if therapy was continued (8.2% versus 3.8% in the discontinued and continued groups respectively, p=0.031).123,124 These results were achieved despite a lack of effect of statins on LDL-cholesterol levels during the same period.

Two studies122,124 investigated the effects of statin withdrawal after ACS by interrogating the National Registry of Myocardial Infections database, a large database of consecutive patients admitted to 1,250 institutions in the USA. Both studies concluded that statin withdrawal was associated with a doubling of the in-hospital morbidity and mortality rates compared with patients in whom therapy was continued.122,124 The GRACE study125,126,128 a clinical trial investigating the relationship of statins in ACS and referred to previously, also indicated that discontinuation of chronic statin therapy was associated with a greater incidence of in-hospital complications and death.

The concern arises that subjects with stable coronary artery disease may also suffer harm following termination of statin therapy. Indeed, the very first indication of harm following statin withdrawal emanated from a New Zealand report, in which changing from an adequate dose of a potent statin to an inadequate dose of a less potent statin increased subsequent thrombotic events threefold.128 Nonetheless, a formal investigation of statin discontinuation in more than 9,000 subjects with stable coronary artery disease did not reveal a subsequent increased incidence of problems.129,130 However, the subjects enrolled in this study were changed from a high to a low dose of statin. This makes it questionable whether this particular study was truly representative of statin withdrawal, and warrants further studies.

Acute loss of benefit following statin withdrawal after stroke

Evidence is accumulating that statin administration before, during or shortly after acute stroke improves subsequent outcome.129,131 Endres and Laufs studiously and eloquently expressed concern regarding statin withdrawal if patients are maintained “nil per os” immediately following stroke.127 Their concern has been fuelled by animal studies suggesting that within a short period of time (two days), withdrawal of statins completely abrogated protection against experimentally induced stroke. However, the subjects enrolled in never received statins, statin withdrawal was associated with a 19-fold (95% CI 1.96 to 184.09) greater risk of early neurological deterioration.128 The authors suggested that these observations confirmed that rebound phenomena occurred after statin withdrawal.

Pathophysiology of statin withdrawal

The mechanisms of the rapid offset of biological effects after abrupt termination of statin therapy are not LDL mediated, but are rather related to rebound pro-inflammatory effects, reduction in nitric oxide production, increased oxidative stress, endothelial dysfunction and hypercoagulability.

Rebound effects and endothelial dysfunction after statin withdrawal

During chronic statin therapy, less substrate is available for the adequate functioning of the isoprene pathway. This results in less isoprenylation and diminished membrane binding of Rho GTPases. In addition, a feedback mechanism promotes Rho gene transcription during statin therapy. The consequence of the aforementioned is accumulation of non-isoprenylated, inactive cytoplasmic Rho. On discontinuation of statin therapy, the functioning of the isoprene pathway is restored. The large amounts of Rho that have accumulated in the cytoplasm again undergo isoprenylation, translocate to the cell membrane and become activated.129 Activation of Rho GTPase inhibits endothelial nitric oxide synthesis.132 This effect has been observed to result in a 90% decrease in murine nitric oxide production two days after statin withdrawal.133,134 Parallels to the rapid decreases in murine nitric oxide production two days after statin withdrawal are rather related to rebound pro-inflammatory effects, reduction in nitric oxide production, increased oxidative stress, endothelial dysfunction and hypercoagulability.
Acute pro-inflammatory responses
While statins exhibit powerful anti-inflammatory effects, withdrawal of the drug accentuates pro-inflammatory processes. Statin withdrawal has been associated with exaggerated expression of a number of pro-inflammatory and proatherosclerotic molecules such as monocyte chemo-attractant protein-1,137 vascular cell adhesion molecule-1,138 interleukin-6 and CRP.134,139,140 These exaggerated responses occur relatively acutely (24 to 72 hours) and are unrelated to changes in LDL-cholesterol levels.134-139 Li and colleagues hypothesised that rebound inflammation occurring after abruptly stopping statin therapy is an important mechanism of plaque destabilisation and subsequent cardiovascular events.139,140

Increased coagulation and decreased fibrinolysis
Within three days of statin withdrawal, and despite unchanged LDL levels,138 increases in the expression of tissue factor VII and decreases in tissue plasminogen activator levels occur.127,137 Activation of Rho GTPase increases (markers of) platelet activation (platelet factor 4 and beta thromboglobulin).93 The net effect of these pro-coagulant effects of statin withdrawal was exemplified by loss of prevention of thrombus formation after aortic occlusion in an animal model.93 The loss of anticoagulant effects observed in this study started only four days after statin withdrawal.

Pharmacokinetics of statins and withdrawal
The elimination half-lives of pravastatin, simvastatin, atorvastatin and rosuvastatin are approximately 1.5, 1.9, 14 and 19 hours respectively.1,12 However, some statins have long-acting active metabolites; for example, atorvastatin has two active metabolites with elimination half-lives of between 20 to 30 hours that account for 70% of its inhibition of HMG-CoA reductase.127,141,142 With the exception of pravastatin and rosuvastatin, the statins are subject to extensive metabolism in the liver and the gut by CYP450 3A4 isoenzymes.143,144 The 20-fold variation in activity exhibited by this enzyme partly explains the highly variable pharmacokinetics of statins.143

Pravastatin and rosuvastatin differ in their pharmacokinetic properties when compared with currently available statins. Neither are extensively metabolised by cytochrome P450 3A4 isoenzymes.144 The kinetics of rosuvastatin are more predictable as this drug does not undergo extensive metabolism and is eliminated largely unchanged. Unlike the other statins, pravastatin employs dual routes of elimination, as the unchanged compound as well as its metabolites is eliminated hepatically and renally.144 The predictable pharmacokinetics and short half-life of pravastatin will likely result in an evanescent effect after discontinuation.145

While it is still not clear whether the effects of withdrawal are dose dependent,147 the consequences of withdrawal will presumably occur more rapidly and with greater severity after termination of statins with a shorter elimination half-life. This hypothesis was not tested in the Le Manich study,148 albeit the Schouten study145 indeed demonstrated that slow-release preparations ameliorated the effects of statin withdrawal. Nonetheless, the following discrepancies between the biological effects and pharmacokinetic half-lives of statins have been noted.139,146

1. Reduction in LDL-cholesterol is not related to the plasma concentration of either statins or their metabolites, but rather to the daily dose of statin.139,148 The reason for this anomaly is that statins are found in the highest concentration in the liver.143,144

2. LDL-cholesterol has a half-life of three to four days, which predicts that LDL levels should reach steady state approximately ten to 14 days after starting statin therapy. However, steady state is usually achieved after approximately double that time. This is proposed to be due to various LDL-cholesterol feedback processes.145

3. The considerations regarding perioperative statin withdrawal are further complicated if we consider that the pleiotropic effects have a significantly more rapid onset and offset than the effects of statins on LDL-cholesterol.127 For example, in a study of hypercholesterolaemic patients receiving low-dose atorvastatin for three months, the 46% decrease in CRP was reversed within only two days of stopping statin therapy, in spite of unchanged LDL-cholesterol levels during this period of time.140

4. In a study of healthy subjects who received high-dose (80 mg) atorvastatin for 30 days, impairment of endothelial-dependent vasodilatation was apparent within 24 hours of discontinuation of the drug.146 This effect was independent of cholesterol levels and the degree of inflammation present.146 This is surprising when considering the long half-life of atorvastatin, but emphasises the powerful effects that rebound has, after statin withdrawal.

Factors contributing to perioperative statin discontinuation
The American Heart Association previously suggested that statin administration may be associated with an increased incidence of perioperative rhabdomyolysis.148 However, only a few case reports and no studies have been published to document this hypothesised increase in risk.148 In an attempt to clarify this risk, Schouten and colleagues149 conducted a retrospective study of 981 vascular surgery patients but could not elicit an increased risk of myopathy. Nevertheless, in the light of the low incidence of myopathy (0.5 to 3.5 per 10 000 patient years)149 and fatal rhabdomyolysis (less than one per million prescriptions),147,148 the aforementioned study was probably underpowered to detect whether an increased incidence of statin associated myopathy occurs in the perioperative period. (The latest American Heart Association guidelines (Guidelines on Perioperative Cardiovascular Evaluation and Care for Non-cardiac Surgery) include a Class 1 recommendation that patients currently taking statins and scheduled for noncardiac surgery should be continued (Level of Evidence: B).)

Other factors related to statin withdrawal perioperatively are the patients’ "nil per os" status, which is likely to occur predominantly in sicker patients, the lack of an intravenous preparation, and communication errors in the intensive care unit. Practical approaches to avoid postoperative statin withdrawal should include:

1. Heightened awareness of the problem.

2. The preoperative administration of slow-release preparations.

3. The administration of statins as soon as possible after surgery, and considering alternative routes if necessary (for example, via a nasogastric tube, sublingually or even rectally).149

4. The development of commercially available intravenous preparations would be useful, although they would be utilised in limited numbers of patients and likely be expensive.

Conclusion
Statins appear to offer significant cardioprotection especially after vascular and coronary artery bypass surgery. However, anaesthesiologists should be aware that omitting statins after surgery has been associated with worse postoperative cardiac outcomes. The deleterious effects of statin withdrawal are likely to be a class effect.127 The postoperative risks associated with discontinuation of these drugs are likely to apply to other types of surgery such as carotid endarterectomy, lower limb revascularisation, coronary artery bypass grafting and patients with previous strokes. In summary, it is inadvisable to discontinue statin therapy postoperatively after any type of surgery, unless specific contraindications, drug interactions or complications of statin therapy co-exist.149

References
1. Ehrenstein MR, Jury EC, Mauri C. Statins for atherosclerosis – as good as it gets? N Engl J Med 2005;352(1):73–5.

2. Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995;91(13):2844–50.

3. Tophi JJ. Intensive statin therapy – a sea change in cardiovascular prevention. N Engl J Med 2004;350(15):1562–4.

4. Ray KK, Cannon CP. Intensive statin therapy in acute coronary syndromes. Clinical
73. Lee JW. Statins and cardiovascular risks. Int Anesthesiol Clin 2005;43(2):55–68.
74. Libby P. Mechanisms of plaque stabilization with statins. Am J Cardiol 2005;96(5A):61F–8F.
75. Kinlay S. Potential vascular benefits of statins. Am J Med 2005;118 (Suppl 12A):62–7.
76. Krupinski JW, McEntee PL, Pugh CM, Selwood SJ. Cholesterol reduction yields clinical benefit: Impact of statin trials. Circulation 1998;97(10):946–52.
77. Aikawa M, Sugiyama S, Hill CC, Voglic SJ, Rabkin E, Fukumoto Y, et al. Lipid lowering reduces oxidative stress and endothelial cell activation in rabbit atheroma. Circulation 1999;99(5):516–21.
78. Aikawa M. Effects of statin therapy on vascular dysfunction. Coron Artery Dis 2001;12(1):49–56.
79. Sugiyama S, Kiyagata K, Aikawa M, Nakamura S, Ogawa H, Libby P. Hypcholesterolemic acid, a macrophage product, induces endothelial apoptosis and tissue factor expression. Am J Pathol 2001;158(6):1977–87.
80. Nakamura M, Sugiyama S, Hill CC, Aikawa M, Libby P, Furukawa Y. Expression of myeloperoxidase is induced in platelet and/or oxidized phospholipid in plaque destabilization and thrombogenesis. Arterioscler Thromb Vasc Biol 2004;24(7):1389–94.
81. Libby P. Evidence of plasma markers of plaque stability. Circulation 2003;108(7):879–81.
82. Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, et al. Lipid lowering reduces oxidative stress and endothelial cell activation in rabbit atheroma. Circulation 1998;97(10):946–52.
83. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: Impact of statin trials. Circulation 1998;97(10):946–52.
84. Okin P, Pfeffer MA, Braunwald E. Statins and cardiovascular risks. Int Anesthesiol Clin 2005;43(2):55–68.
85. Nissen SE. Effect of intensive lipid lowering on progression of coronary artery disease: Five years after HINS. Circulation 1999;99(15):1947–57.
86. Nissen SE. Halting the progression of atherosclerosis with aggressive lipid lowering: Evidence for an early benefit from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. Am J Cardiol 2005;95(6A):61F–8F.
87. Nicholls SJ, Tuzcu EM, Spilki J, Schoenhagen P, Hazen SL, Ntanios F, et al. Effects of cholesterollowering, anti-inflammatory, and anti-platelet agents on lipid, macrophage and endothelium in human carotid atherosclerosis. J Biol Chem 1997;272(50):31725–9.
88. Ruprich B, Pfeffer MA, Braunwald E. Statins and cardiovascular risks. Int Anesthesiol Clin 2005;43(2):55–68.
89. Libby P. Evidence of plasma markers of plaque stability. Circulation 2003;108(7):879–81.
90. Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, et al. Lipid lowering reduces oxidative stress and endothelial cell activation in rabbit atheroma. Circulation 1998;97(10):946–52.
91. Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, et al. Lipid lowering reduces oxidative stress and endothelial cell activation in rabbit atheroma. Circulation 1998;97(10):946–52.
92. Libby P. Evidence of plasma markers of plaque stability. Circulation 2003;108(7):879–81.