Statins and perioperative myocardial infarction: Mechanisms of action

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ABSTRACT
The growing prevalence of atherosclerosis means that perioperative myocardial infarction (PMI) is a significant issue for the anesthesiologist. Perioperative revascularization (if indicated medically), beta blocker (in high risk patients) and statin therapy are therapeutic modalities that are currently employed to reduce PMI. Statins not only lower low density lipoprotein levels but, via their actions on the isoprene pathway, also exhibit pleiotrophic effects anti-inflammatory effects, thereby stabilizing vulnerable plaque and improve functioning of the endothelium in atherosclerosis. These effects appear to reduce perioperative complications of atherosclerotic lesions. It is important to have an understanding of newer developments in the pathophysiology of atherosclerosis to be able to appreciate the mechanisms of action of statins. The focus has changed from identification of stenotic coronary lesions to the identification of vulnerable plaque. This review is divided into 2 parts. The first part focuses on the pathophysiology of atherosclerosis while the second part discusses the pharmacology of statins and the mechanisms of how they may reduce PMI.

Introduction
Statins are currently unsurpassed in secondary and primary prevention of complications from atherosclerotic vascular disease.1 The first study to conclusively demonstrate benefits from statin usage was the Scandinavian Simvastatin Survival Study (The 4s trial).2 This and subsequent studies have lead to a new insights into the pathophysiology of coronary artery disease and an explosion in the use of this class of drugs.3 At the time of the original studies demonstrating the benefit of statins in limiting complications of vascular disease, it was considered that the predominant effect of statin therapy was linked with reduction in low density lipoprotein cholesterol (LDL cholesterol) levels.4,5 A 10% reduction in LDL cholesterol was linked to a 10% reduction in cardiovascular risk.

However, subsequent studies (for example, the Heart Protection Study, the Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)3-5 and the Pravastatin or Atorvastatin Evaluation and Infection Therapy -Thrombolysis In Myocardial Infarction 22 (PROVE IT TIMI 22)6-11 trials), although confirming the benefits of these drugs and supporting aggressive lipid lowering strategies, raised new questions because the benefit of statins appeared to be more than simply reduction in LDL cholesterol.12 Subjects, who initially had high LDL cholesterol levels and also those with LDL cholesterol levels within the normal accepted range, both received as much benefit from statin therapy.1 This raised the question whether the non-lipid lowering effects are important mechanisms governing outcomes with statin therapy.12-15 Indeed, inflammation is an important driver of atherosclerotic processes. Having greater degrees of inflammation present, as demonstrated in the Cholesterol and Recurrent Events (CARE), Arterial Biology for the Investigation of Atherosclerosis (AB-IT),6 West of Scotland Coronary Prevention Study (WOSCOPS)16 and other studies,17-19 have been shown to be a powerful predictor of future cardiovascular events.12-20 In the light of the foregoing, a critical question arises whether inflammatory markers such as ultra sensitive C reactive protein levels, can be useful to select patients that can benefit from statin therapy independent from their LDL cholesterol levels.21 This is the hypothesis driving the JUPITER trial that is currently in progress.

The PROVE-IT TIMI 2210;11 and Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL)22-25 studies have suggested that the use of early high dose statin therapy may have relatively early benefits as they reduce adverse cardiovascular events after acute coronary syndromes.26 Recent meta-analyses indicate that statins protect patients from perioperative myocardial infarction in the perioperative period. In this review, the mechanisms of action especially the non-lipid lowering effects whereby statins reduce inflammation, facilitate plaque stability and improve endothelial function will be emphasized.27,28

Mechanisms of action of statins
An important function of statin therapy is to lower LDL cholesterol levels. This combined with the non-cholesterol lowering (pleiotropic) effects, benefit endothelial function with greater expression of endothelial nitric oxide, reduced clotting and inflammation that stabilizes atherosclerotic plaques at risk of rupture. It is sometimes difficult to separate the LDL cholesterol lowering from the pleiotropic effects but, for clarity, we shall do so in this review. It is of relevance to the anesthesiologist that, in the short term, the non-LDL cholesterol independent pleiotropic (predominantly anti-inflammatory) effects of statins predominate.15

Reduction of LDL cholesterol levels
Mechanisms whereby LDL cholesterol is reduced
“Statins” are a group of drugs that concentrate in the liver and inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.27 The first selective inhibitor of HMG-CoA reductase was reported by Endo and colleagues in 197628 with Alberts subsequently isolating a much more potent agent, lovastatin, from a fungus as recently as 1988.29 HMG-CoA reductase is the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in the synthesis of cholesterol, bile acids, vitamin D, steroid hormones and also elements of the isoprene pathway.30,31 An important clinical consequence of statin administration is lowering of LDL cholesterol levels.32 Nonetheless, cholesterol is an important component of cell membranes and therefore, greater numbers of LDL receptors are expressed on cell surfaces in an attempt to absorb more of the available LDL cholesterol.32-35 Statins also further the
cancellation of LDL cholesterol because of an increase in the number of hepatocyte LDL surface receptors. These receptors are responsible for the uptake and catabolism of LDL cholesterol. The result is that plasma LDL cholesterol levels can be reduced by as much as 50 to 60% by statin therapy.5,52 Statins also increase HDL levels by 5 to 10%, and although this increase is marginal, it may well improve removal of LDL cholesterol and macrophage foam cells from vascular endothelium.38,39

Consequences of reduction in LDL cholesterol

Reduction in LDL cholesterol results in less LDL cholesterol being present and prevention of further progression of atherosclerotic plaques. There are indeed studies demonstrating plaque regression if LDL cholesterol is very greatly reduced. All this translates into a decrease in cardiovascular complications of atherosclerotic disease.36,38,39 However, one of the more important consequences of preventing complications from atherosclerotic plaques is to stabilize them, rather than shrink them. Experimental animal work by Libby and co-workers has demonstrated that reduction in LDL cholesterol levels does indeed improve stability of vulnerable plaque for the following reasons:40

1. A decrease in cholesterol deposition in plaques
This decreases atherosclerotic plaque size and wall tension making the plaque less vulnerable to rupture.41

2. Improved endothelial expression of nitric oxide synthetase and nitric oxide expression.
The adverse effects of raised LDL cholesterol levels on the vascular endothelium can appear, but also regress, very rapidly.42,43 It has been shown in cell culture that increasing LDL cholesterol reduces nitric oxide expression significantly within 60 minutes. However, rapidly lowering LDL cholesterol by employing apheresis, promptly restores nitric oxide levels and endothelial mediated vasodilatation.

3. Reduction of endothelial inflammation
Lowering LDL cholesterol also results in less endothelial inflammation. The anti-inflammatory effects are related to the lower levels of LDL cholesterol and oxidised LDL, but also to better functioning of the endothelium, especially greater levels of nitric oxide. It is important to appreciate that nitric oxide is not only a vasodilatory agent, but also possesses atheroprotective and anti-inflammatory properties. This is because nitric oxide decreases endothelial cell over-expression of leukocyte adhesion molecules, especially vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, Rho, Ras and Rac.44 These isoprene chains serve as lipid attachments that allow these G-proteins to attach to the inside of the cell membrane and then act as molecular switches to simultaneously coordinate the activation of a wide variety of intracellular processes.38 Isoprenylation regulates transcription factor activity, facilitates covalent attachment, subcellular localization, and membrane trafficking of cytoplasmic proteins.55-57 Therefore, inhibition of isoprenylation results in accumulation of Rho and Rac in the cytoplasm. This leads to changes in the actin cytoskeleton of the cell and subsequent alterations in intracellular signaling processes, transcription, subcellular localization and membrane trafficking of cytoplasmic proteins.58 Isoprenylated Rho activates nuclear factor kappa beta (NFKB) in endothelium, platelets and leucocytes.59-60 Activated NFKB increases nuclear transcription of pro-inflammatory cytokines such as monocyte chemo-attractant protein-1, interleukin-1, interleukin-8, interferon-gamma, metalloproteinases, matrix metalloproteinase-9 (MMP-9) and matrix metalloproteinase-12 (MMP-12).36,61-64 The result is that fewer macrophages become adherent to the endothelium, endothelial adhesion of leukocytes being a hallmark of inflammation.42 If fewer leucocytes are adherent to the endothelium, this means that fewer macrophages migrate into and are present in the intima and there is reduced production of cytokines and matrix metalloproteinases.45-48 These mechanisms limit vascular endothelial and intimal inflammation,49 which reduces expression of oxygen radicals, causes less T lymphocyte production of interferon, less monocyte activation, less apoptosis of smooth muscle cells and greater production of collagen and elastin.46 Greater amounts of smooth muscle cells result in more collagen being present in plaques which enhances the strength of the fibrous cap.

4. Decreased thrombogenicity.
A decrease in LDL cholesterol reduces endothelial and intimal inflammation reducing expression of factor 7 while improving nitric oxide production.49 Decreasing LDL levels also reduces excessive platelet aggregation.45,47

The pleiotropic effects of statins

While the decreased cardiovascular morbidity and mortality demonstrated by the Scandinavian Simvastatin Survival Study (the “4s” study) was originally attributed to reduction in cholesterol levels,59,60,61,62 it has since become apparent that statins have significant beneficial effects on cardiovascular morbidity and mortality long before the lipid profile has improved. Furthermore, the degree of benefit achieved significantly exceeds that expected from reductions in LDL cholesterol alone.41 A search for the answer to this phenomenon has revealed that the inhibition of HMG-CoA reductase by statins also results in inhibition of the inflammatory pathway in endothelial cells, vascular smooth muscle and inflammatory cells (monocyte-macrophage system) and this leads to non-LDL mediated benefits in atherosclerosis.36,39 The multiple non-LDL mediated effects of statins predominantly promote anti-inflammatory and anti-coagulant processes. This results in less inflammation, greater endothelial health and ultimately, greater plaque stability. The plethora of non-LDL effects have been called the “pleiotropic” effects of statins.41,51 (The word “pleiotropy”, which is 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.49) That the pleiotropic effects of statins are dose dependent and occur within hours of administration, is potentially of great importance to anesthesiologists.31

The isoprene pathway is a biochemical entity that is unfamiliar to most anesthesiologists. The reason why statins have an isoprene pathway functioning is that HMG CoA reductase inhibition causes inadequate amounts of farnesyl and geranylgeranyl pyrophosphate to be available for it to function in a standard manner. The role of the isoprene pathway is to add isoprene chains (termed isoprenylation) to small G-proteins (also called GTPases). Rho, Ras and Rac.59 These isoprene chains serve as lipid attachments that allow these G-proteins to attach to the inside of the cell membrane and then act as molecular switches to simultaneously coordinate the activation of a wide variety of intracellular processes.38 Isoprenylation regulates transcription factor activity, facilitates covalent attachment, subcellular localization, and membrane trafficking of cytoplasmic proteins.55-57 Therefore, inhibition of isoprenylation results in accumulation of Rho and Rac in the cytoplasm. This leads to changes in the actin cytoskeleton of the cell and subsequent alterations in intracellular signaling processes, transcription, subcellular localization and membrane trafficking of cytoplasmic proteins.59-61 Other downstream effects of NFKB inhibition include inhibition of plasminogen activator inhibitor-1 and expression of vascular endothelial cell growth factor in endothelial cells.60 Statins are also responsible for preventing T-lymphocyte activation by decreasing expression of important major histocompatibility complexes.62 The above actions of statins all promote stability of vulnerable atherosclerotic plaques.

By limiting inflammation, statins reduce endothelial cell expression of adhesion molecules, selectins and intracellular adhesion molecule-1, both in hypercholesterolemic patients and also after ischemia and reperfusion. In addition, statins reduce expression of adhesion molecules expressed on the surface of leucocytes that allow them to interact with endothelial cells.63,64
of the interaction with the endothelium limits subsequent leukocyte trafficking in areas of inflammation.

This has the effect of limiting damage in inflamed and damaged tissue. Note that these effects of statins are nitric oxide dependent as they are not present in eNOS deficient mice.

A further consequence of the inhibition of the isoprene pathway is that there is more limited expression of a subset of cytokine receptors, the chemokine receptors, on the surface of cells. Chemokines and cytokine receptor expression play a crucial role in the inflammation that characterizes atherosclerosis. OCT 1 is a protein that inhibits mRNA-dependent translation of cytokine receptors (i.e. it is a translational repressor). Isoprenylation inhibits OCT 1, thus permitting the translation of cytokine and chemokine receptors to carry on unfettered. This dose dependent inhibition occurs in both macrophages and endothelial cells and has convincingly been shown to be dependent on HMG CoA reductase as it is inhibited by administering mevalonate.

However, statins, by decreasing isoprenylation and decreasing the inhibition effected by OCT 1, inhibit the expression of chemokine receptors 1 – 5.

Statins improve endothelial vasodilator function. Experimentally, this is seen as improved flow mediated vasodilatation, a process governed by expression of nitric oxide. Improvement of endothelial vasodilator function involves two mechanisms. The first involves reduction in LDL cholesterol while the second mechanism is likely to be a consequence of isoprene pathway inhibition. Nitric oxide synthetase (eNOS) largely resides in clefts called caveolae that are present in the luminal surface of endothelial cells. ENOS can bind to an inhibitory protein called caveolin in the membrane of the caveolae or to a calcium-calmodulin complex that activates it. In normal endothelium, shear stress causes phosphorylation of enzymes that increase the calcium-calmodulin complex competition for, and activation of, eNOS. On the other hand, hyperlipidemia increases caveolin. Statins improve the function of eNOS because they both decrease LDL cholesterol levels and also directly disrupt the endothelial actin cytoskeleton reorganization and expression of factor 7.

Statins also demonstrate anti-thrombotic and pro-fibrinolytic effects. Inflammatory mediators cause macrophages, smooth muscle, and endothelial cells to over-express tissue factor. Statins reduce the stability of AT1 mRNA and by limiting isoprenylation of Rac, prevent it from attaching to the cell membrane and activating NADPH oxidase.

Surprisingly, the mechanism whereby the statins increase eNOS concentration is not because of induction of eNOS transcription. Rather it involves statins induced inhibition of Rho isoprenylation which disrupts the endothelial actin cytoskeleton reorganization and thereby stabilizes eNOS mRNA. This work as follows. The actin cytoskeleton provides the framework for cell shape and movement of cells including endothelial cells. mRNA needs to anchor to the actin cytoskeleton firstly to ensure its stability and secondly, to be in close proximity (co-localized) with ribosomes for translation to be successful. Isoprenylation of Rho is a prerequisite for translocation of the inactive G protein Rho into the cytoplasm. Isoprenylated Rho binds to and activates Rho associated GTPases. This leads to phosphorylation of myosin light chain kinases with consequent reorganization of the actin cytoskeleton. The Rho controlled reorganization of the cytoskeleton appears to play an important role in the subcellular location of specific mRNAs within the cell. This reorganization however, inhibits eNOS anchoring to the cytoskeleton and its subsequent stability and ability to produce mRNA.

Via this mechanism increases the half life of eNOS mRNA from 13 to 38 hours which translates into a 3 fold greater production of nitric oxide. The aforementioned mechanism is of clinical significance because hypoxia, LDL cholesterol and cytokines all decrease the stability of eNOS mRNA. Indeed, the nitric oxide preserving effects of statins seem to be important in preserving tissue in at least two vital organs, the brain and the heart.

Enhanced endothelial nitric oxide production results in increased cerebral blood flow after cerebral ischemia following statin administration. This has been linked to neuroprotection in experimental stroke in animals.

Statin therapy has also been shown to be cardioprotective in that it attenuates reperfusion injury after ischemia in an animal model. Statin pretreatment resulted in 41% less myocardial necrosis and 62% reduction in neutrophil infiltration in the reperfused area. Limiting neutrophil infiltration and thereby the inflammation, has been shown to reduce myocardial injury after ischemia-reperfusion. Statin therapy further limits reperfusion injury because enhanced nitric oxide production inhibits the activation of NFkB, reduces release of cytokines and cellular adhesion molecules with attenuation of neutrophils to the endothelium.

Another recent and noteworthy observation is that statins reduce the myocardial no-reflow phenomenon after ischemia and reperfusion by activating mitochondrial K(ATP) channels.

Interestingly, improvement in endothelial function may well be one of the earliest consequences of starting statin therapy. Initially, increases in nitric oxide were thought to take 4 to 6 weeks to be realized. However, a number of studies have demonstrated improvement in flow mediated endothelial dependent vasodilatation within 3 hours.

The Rho controlled reorganization of the actin cytoskeleton results in increased which favors clotting. Statins inhibit plasminogen activator inhibitor-1 expression by vascular endothelial and smooth muscle cells which restores the balance in favor of fibrinolysis.

Oxygen radicals such as superoxide, the hydroxyl radical and reactive oxygen species such as hydrogen peroxide, peroxynitrite and hypochlorous acid all inactivate nitric oxide. There are several sources of oxygen radicals in endothelial cells including xanthine oxidase, eNOS and membrane bound NADPH oxidase. Although angiotensin II, thrombin, platelet derived growth factor and tumour growth factor alpha all stimulate NADPH oxidase, the most important mechanism of radical production involves angiotensin activation of the angiotensin AT1 receptor and subsequent NADPH oxidase activation. Statins reduce the stability of AT1 mRNA and by limiting isoprenylation of Rac, prevent it from attaching to the cell membrane and activating NADPH oxidase.

Statins themselves, have also been demonstrated to scavenge oxygen radicals, including superoxide and the hydroxyl radical, in a dose dependent manner. Reduction in levels of oxygen radicals promotes the bioavailability of nitric oxide and adds to the tissue sparing effects of statins in reperfusion injury and contribute to amelioration of endothelial dysfunction.

Statins also demonstrate anti-thrombotic and pro-fibrinolytic effects. Inflammatory mediators cause macrophages, smooth muscle and endothelial cells to over-express tissue factor. Tissue factor plays a pivotal role in thrombus formation in myocardial infarction. Because of the inhibition of the isoprene pathway and anti-inflammatory properties of statins, there is less activation of macrophages which results in less expression of tissue factor.

In addition, less activation of Rho results in better endothelial cell function and greater thrombomodulin expression. In atherosclerosis, the ratio of plasminogen activator inhibitor-1 to tissue plasminogen activator increases which favors clotting. Statins inhibit plasminogen activator inhibitor-1 expression by vascular endothelial and smooth muscle cells which restores the balance in favor of fibrinolysis.

Greater expression of nitric oxide in the presence of statins will also inhibits platelet aggregation, an effect that is emphasized by lowering of LDL cholesterol levels.
Libby and others\(^{109,110}\) have used a cynomolgous monkey model fed an atherogenic diet to compare statin therapy with diet modification for amelioration of atherosclerosis. The lipid levels of both the statin treated and the placebo group were maintained at similar levels. They have observed that statin therapy produced cholesterol independent improvement in the plaque biology.

Specifically they and others have demonstrated that statins reduce the expression of vascular cell adhesion molecules, reduce macrophage infiltration into the endothelium, reduce the expression of matrix metalloproteinases by the monocyte macrophages, reduce the expression of interleukin-8, increased smooth muscle cell content of atheromata, reduces expression of tissue factor and improves endothelial function in atherosclerotic lesions.\(^{110,111,112}\) These endpoints, which are beneficial for reducing plaque inflammation, promoting their stability and preventing rupture are more rapidly achieved after statin therapy than after diet modification with similar LDL cholesterol lowering end points.\(^{113}\) This is evidence that the non-LDL mediated effects of statins are indeed significant in plaque stabilization.

The relative importance of LDL cholesterol lowering versus the pleiotropic effects of statins has been debated in the literature. What is clear at this time is that reduction in LDL cholesterol represents a late benefit, while the pleiotropic effects represent an early benefit to the patient. How early this benefit occurs is of great relevance to perioperative medicine.

In summary, inhibition of the isoprene pathway and also lowering of LDL cholesterol by statins has 3 main consequences in atherosclerotic tissue.

1. Statin therapy reduces inflammation, an important promoter of the atherosclerotic process and a process that makes plaques vulnerable to rupture.
2. Endothelial dysfunction is improved.
3. Statin therapy lowers the risk of thrombosis and facilitates fibrinolysis.

**Evidence that perioperative statin therapy reduces perioperative cardiovascular events**

Reduction of perioperative complications by statin administration represents a significant issue in contemporary anesthesia literature and a number studies, 2 recent meta-analyses\(^{67,68}\) and reviews\(^{56,69,70,71}\) of the topic have been published recently. In 2005, Biccard and colleagues\(^{69}\) reviewed 8 studies\(^{90,116}\) investigating the effects of statins in non-cardiac surgery and more\(^{109,110,113}\) have been published since that particular review. Although the majority of the studies (excluding the Lindnauer study) have been small retrospective studies, they have mostly studied high risk vascular surgery patients and they have indeed demonstrated significant benefits in terms of perioperative cardiovascular mortality and morbidity. A number of studies have also demonstrated that statins are useful therapy before and after coronary artery bypass grafting.\(^{125,129}\) Hindler and colleagues’ meta-analysis indicate that one can expect a 39% and a 50% reduction in mortality after cardiac and non-cardiac vascular surgery respectively. In the meta-analysis performed by Kapoor and co-workers\(^{2}\), the odds ratio for a combined end-point of death and acute coronary syndrome was 0.7 for both cardiac and non-cardiac surgery. This latter meta-analysis nevertheless, criticized the non-randomization of the studies and reported that “the evidence base that statins indeed reduce perioperative cardiovascular risk is inadequate.”\(^{12}\) It is important to note that no meta-analysis has as yet come to the conclusion that statins do not help or are indeed dangerous in the perioperative period. Furthermore, statins also appear to be “more cost effective after vascular surgery than primary and secondary prevention of coronary artery disease.”\(^{120,121}\)

The endpoints in the majority of the studies have been cardiac death, non-fatal myocardial infarction, unstable angina pectoris or stroke. These represent reasonable endpoints in that they are likely complications of atherosclerotic disease and can be explained by perioperative plaque ruptures or fissuring with thrombus formation, myocardial ischemia and infarction. Another speculative mechanism whereby statins may reduce perioperative complications is via their anti-inflammatory effects. The inflammatory response that follows surgery results in high levels of cytokines such as tumor necrosis factor alpha, interleukin-1, interleukin-6, interleukin-8 and CRP. This response may well have a role to play in destabilizing plaques and lead to delayed PMI\(^{132}\), it is proposed that statins may play a role by limiting this process.

The meta-analysis performed by Hindler and colleagues demonstrated a lower stroke rate in vascular surgery patients on statin therapy (2.0 versus 3.3%, \(p = 0.049\)), but not after cardiac surgery.\(^{12}\) This conclusion was arrived at predominantly because of findings made in a single study.\(^{18}\) Nonetheless, this finding is not surprising as the pathophysiology of stroke and coronary artery disease is not very different.\(^{133}\) Inflammation is likely to cause widespread plaque instability, linking instability in coronary peripheral vascular lesions and carotid plaques.\(^{134}\)

**Questions still exist regarding statin therapy in the perioperative period**

A vexing question that still needs to be answered is how long before surgery does statin therapy need to be commenced to prevent perioperative plaque rupture? The earliest that statins were administered in any of the studies included in the meta-analyses was 30 days before surgery.\(^{164}\) However, although plaque stabilization does occur with statin therapy, this may well take a few weeks to occur.\(^{130}\) What is apparent is that endothelial vasodilator function is restored quickly after therapeutic levels of statin have been achieved. Dotani and colleagues\(^{69}\) demonstrated greater coronary blood flow in both bypassed and non-bypassed segments after only 4 days statin treatment before coronary bypass grafting. It is likely that the increased expression of nitric oxide was responsible for at least part of the benefit seen by these patients soon after statin administration.

The Decrease IV study\(^{135}\) is currently addressing the question whether the combination of beta adrenoceptor blockers and statins have added benefit in reducing the number of perioperative cardiac events. The theory is that beta blockers will prevent ischemia and infarction from mechanical stressors that lead to immediate postoperative myocardial infarctions.\(^{135}\) Beta blockers have also been suggested to reduce postoperative myocardial infarction by an anti-inflammatory effect.\(^{135}\) This is an interesting and potentially important question and it will take approximately four years to complete the study.

Which is the best statin to use perioperatively? Not all statins have similar effects on reducing LDL cholesterol levels.\(^{3}\) For example, although atorvastatin is extremely effective in lowering LDL-cholesterol, it does not increase high-density lipoprotein-cholesterol as much as simvastatin.\(^{136,137}\) This may be important in the removal of cholesterol from plaque. There may also be differences between statins in terms of their pleiotropic effects. An example of this is that all statins powerfully inhibit apoptosis of smooth muscle cells in atherosclerotic plaque, thereby improving plaque stability. However, pravastatin seems to be superior to simvastatin and lovastatin in this respect.\(^{137}\)

The American Heart Association Clinical Advisory on the use of statins recommended that statins be withdrawn in the perioperative period.\(^{138}\) However, acute withdrawal of statin therapy can induce acute coronary syndromes and increase mortality sevenfold in such patients.\(^{128,129}\) The mechanism appears to be activation of NADPH oxidase by Rac and generation of excess levels of superoxide anion and decreased expression of nitric oxide.\(^{141}\) In the light of this, it is the opinion of the authors of this review that it is unwise to stop statin therapy in the perioperative period. Indeed, there are theoretical
indications to initiate statin therapy preoperatively in certain high risk groups.

Further questions regarding perioperative statin therapy that at present remain unanswered include:
1. Who should get statin therapy perioperatively? Should only higher risk patients as suggested by Lindenauer in the beta blocker study or is the risk benefit ratio for statin therapy different?
2. What dosage of statin should be used? There is no known answer to this question and the dosages differ widely between studies.
3. Can anesthesiologists use the degree of inflammation (i.e. ultrasensitive CRP levels) to estimate the extent of vulnerable plaque and thus which patients should get statins perioperatively?

Other uses of statins of relevance to the anesthesiologist

Albeit the therapeutic uses of statins in the perioperative period are mainly for cardiac protection, their anti-inflammatory effects, beneficial effects on the endothelium and plaque stability imply that they have a wider role to play in organ protection.

1. **Statins in inflammatory conditions**

The anti-inflammatory state that follows HMG CoA reductase inhibition may be of relevance not only in atherosclerosis, but also in the management of vasculitides, diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, glomerular nephritis and multiple sclerosis. Patients with rheumatoid arthritis demonstrated a modest but clinically relevant effect after statin therapy. In patients with chronic inflammatory renal disease, statins slow progression of the disease. Statins may well be useful after cardiac (but not renal) transplantation to reduce the incidence of rejection and coronary vasculopathy.

2. **Sepsis**

A number of studies have demonstrated better survival in statin treated animals. Almog and colleagues found that therapy with statins for 1 month before the onset of an acute bacterial infection was associated with a reduced rate of severe sepsis and ICU admission. Almog hypothesized that the diverse immunomodulatory, anti-inflammatory and anti-apoptotic effects on top of the beneficial effects of statins on endothelial function, may be responsible for this result.

3. **Hypertension**

Statins improve endothelial expression of nitric oxide, reduce endothelin release and cause downregulation of angiotensin 1 receptors. Clinically this is seen as a decrease in blood pressure in hypertension.

4. **Pulmonary hypertension**

The beneficial effects of statin therapy on endothelial function and apoptosis confer potentially beneficial effects of these drugs in pulmonary hypertension.

5. **Coronary stenting**

Patients with coronary stents and a high degree of inflammation as measured by ultrasensitive C reactive protein, benefited from statin therapy. Mortality after stenting was reduced from 14.8% to 5.7% by statin pretreatment if the ultra sensitive CRP was greater than 1.11 mg/dl.

6. **Cardiac failure**

Statin therapy has been shown to improve outcome significantly, independent of whether patients had underlying ischemic heart disease or not.

7. **Cerebral ischemia**

Outcome in experimental stroke is improved. Furthermore, it has recently been recognized that vasospasm is attenuated after subarachnoid hemorrhage both in animal and human studies.

8. **Prophylaxis of atrial fibrillation after thoracic and cardiac surgery**

Atrial fibrillation, the most common arrhythmia after cardiac surgery, generally starts on day 2 to 3 postoperatively. This corresponds with the peak inflammation, gene expression and fluid mobilization. Elevated preoperative CRP levels are associated with postoperative atrial fibrillation. One week of atorvastatin therapy before cardiac surgery reduced the incidence of postoperative atrial fibrillation from 5% to 3.5%. Recently, statin administration before thoracic surgery has been shown to decrease the incidence of postoperative atrial fibrillation threefold.

**Safety of statin therapy**

1. **Hepatic function**

For reasons that are currently unknown, hepatic transaminase levels increase within three months of initiation of therapy in one in a 1000 patients or 110 per 100 000 patient years. It is usually reversible on termination of therapy. If statins are initiated, hepatic enzymes should be measured within 3 months of initiation of therapy. It is interesting that a lower incidence of liver disease has been reported in patients taking statins than control subjects. The incidence of liver failure is very small (one per million patient years) in subjects taking statins.

2. **Myopathy**

The incidence of myopathy is 11 per 100 000 patient years and that of rhabdomyolysis is 1.6 to 3.4 per 100 000 patient years. Rhabdomyolysis carries a 10% mortality rate from renal failure. It is especially associated predominantly with co-administration of agents that inhibit cytochrome P450 3A4 (erythromycin or azole antifungal agents) and to a lesser degree, gemfibrozil.

In the light of the controversial American Heart Association Clinical Advisory advising perioperative withdrawal of statins, Schouten investigated the incidence of perioperative myopathy. This study enrolled 981 patients of which 211 were administered statins. No increase in myopathy was detected perioperatively. However, it is doubtful whether the Schouten study, with its limited number of subjects, has the power to determine an association between statins and an increased incidence of perioperative myopathy.

3. **Drug interactions**

The majority of statins except pravastatin and fluvastatin are oxidized by the hepatic cytochrome P450 3A4 system. Induction or inhibition leads to interference with metabolism of statins or other drugs. (For a comprehensive and clear review of drug interactions with statins, see the article by Bellosta and colleagues.)

**Conclusion**

The nascent practice of perioperative statin administration with the aim of reducing perioperative cardiovascular and other complications promises to affect the practice of anesthesiologists in the future. However, there are many questions in this rapidly growing field that still remain to be answered.

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