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Statins for all: the new premed?

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The use of statins is widespread and many patients presenting for surgery are regularly taking them. There is evidence that statins have beneficial effects beyond those of lipid lowering, including reducing the perioperative risk of cardiac complications and sepsis. This review addresses the cellular mechanisms by which statins may produce these effects. Statins appear to have actions on vascular nitric oxide through the balance of inducible and endothelial nitric oxide synthase. The clinical evidence for these benefits is also briefly reviewed with the objective of clarifying the current status of statin use in the perioperative period. There is reasonably strong evidence that patients already taking statins should continue on them perioperatively. However, the evidence for the prophylactic use of statins perioperatively is weak and lacks prospective controlled studies.

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The therapeutic use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, has become widespread. Increasing numbers of patients presenting for surgery, particularly those awaiting cardiac or vascular surgery, are taking statins regularly. There is evidence that statins have beneficial anti-inflammatory actions beyond their lipid-lowering effects, particularly in relation to the incidence of sepsis and cardiovascular complications in the perioperative period. This has led to the suggestion that 'at risk' patients should be treated with statins before operation.

The aim of this review is to assess the scientific and clinical evidence regarding the anti-inflammatory actions of statins and to attempt to put this into the context of perioperative therapeutic use. We will describe the mechanistic role of nitric oxide (NO) in beneficial pleiotropic effects, particularly during coronary artery disease and sepsis, which are of relevance to the anaesthetist or intensivist considering the use of statins as premedication or pretreatment and question whether suggested effects are representative of improvements in mortality.

Therapeutic action (clinical studies)

Statins are lipid-lowering drugs which act by inhibiting hepatic conversion of HMG-CoA to L-mevalonate and subsequent production of the isoprenoid geranylpyrophosphate (Fig. 1). Five statins are currently licensed for use in the UK: atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. The most commonly prescribed statins are atorvastatin and simvastatin. The statins can be further classified into lipophilic (atorvastatin, simvastatin, and fluvastatin) or hydrophilic (pravastatin and rosuvastatin).

Statins reduce low-density lipoprotein (LDL) in the body and also plasma triglycerides and apolipoprotein B.[41] There is also some evidence that they may increase high-density lipoprotein (HDL).[41] In simple terms, LDL increases fatty deposits and plaque formation (atherosclerosis) on arterial walls, which is an initial step in coronary artery (heart) disease (CAD/CHD).[55] The initial Harvard Atherosclerosis Reversibility Project (HARP) studied 79 patients with CHD who had normal plasma cholesterol profiles and allocated them randomly to receive treatment with pravastatin or placebo. Although pravastatin reduced mean total plasma cholesterol from >5.5 to <4.1 mmol, no difference in coronary atherosclerosis was observed between the treatment and the placebo groups over 2.5 yr. The degree of coronary artery narrowing was similar.[62] However, several subsequent clinical trials have presented convincing evidence that statins reduce LDL in conjunction with decreased coronary artery plaque size.[52 77] Clinical studies have also now shown that statins reduce the incidence of coronary events and stroke, and improve survival rates in CHD patients. The West of Scotland Coronary Prevention Study,[79] a

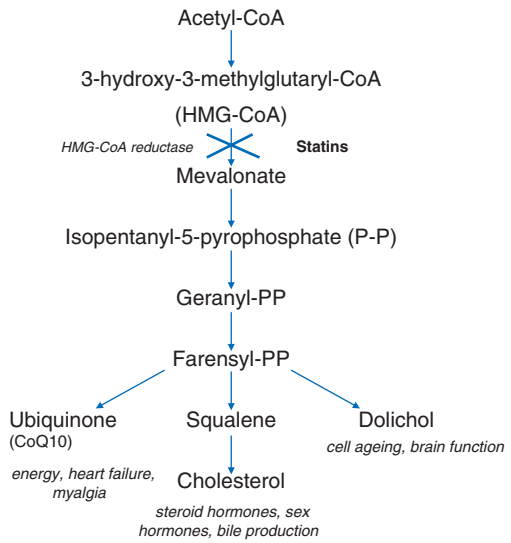

Fig 1 The mevalonate pathway. Statins inhibit production of HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate and thus prevent downstream cholesterol, ubiquinone-, and dolichol-dependent effects. Activity of the small GTPase Rho depends upon geranylation by the isoprenoid geranylgeranyl-PP and is therefore blocked by statins.

primary prevention trial, determined that pravastatin 40 mg day^{-1} reduced morbidity and mortality in CHD in patients with moderate hypercholesterolaemia. The UK MRC/BHF Heart Protection Study[22] enrolled 20 536 patients (aged 40–80 yr) with coronary disease or other occlusive arterial diseases and determined that simvastatin 40 mg daily reduced the rates of myocardial infarction and stroke by about one-quarter. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial enrolled 4731 patients to investigate 5 yr treatment with atorvastatin 80 mg daily and reported a decrease in ischaemic stroke of 21%.[5] Furthermore, a non-randomized study of 551 patients with systolic heart failure, 45% of whom had CAD and were receiving statin therapy, demonstrated improved survival rates from ischaemic and non-ischaemic heart failure in the patients taking statins.[26] Other trials have shown that the beneficial effects of statins may occur after relatively short periods of treatment, for example, 63 patients with non-ischaemic cardiomyopathy given simvastatin 5 mg day^{-1} for 14 weeks experienced increased left ventricular ejection fraction compared with those on placebo.[53]

Pleiotropic effects

The lipid-lowering effects of statins in relation to reduced coronary artery disease are therefore well established and supported by prospective clinical trials, but it became apparent that reduced LDL was not wholly responsible for the beneficial effects in CHD.[3] For example, in the WOSCOPS study,[79] patients with similar intermediate LDL concentrations [i.e. in the overlap between the treated (pravastatin) and the placebo groups], the statin group had better outcomes that could not be explained by differences in LDL. Statins also have anti-inflammatory properties, exemplified by reduced plasma concentrations of the inflammatory cytokines tumour necrosis factor (TNF)-α and interleukin (IL)-6 in patients receiving pravastatin.[53] This has been highlighted most recently by the JUPITER trial, where rosuvastatin reduced the incidence of myocardial infarction, stroke, or death from cardiovascular causes in patients without hyperlipidaemia but with elevated high-sensitivity C-reactive protein levels.[59] Statins are also effective in lipid-independent conditions, such as sepsis, decreasing mortality rates in intensive care units;[18] nephropathy, decreasing the rate of renal damage in diabetics;[76] Alzheimer's disease and dementia, decreasing incidence and progression;[29 70] autoimmune disease, demonstrating beneficial effects in rheumatoid arthritis;[38] organ transplantation, decreasing rejection rates;[44] gastrointestinal disease, possibly decreasing the incidence of colon cancer[57] and inflammatory bowel disease;[64] osteoporosis;[6] and macular degeneration.[33] There is an apparent common factor within these disease processes of an inflammatory basis. However, one study has demonstrated that lipid lowering may be more important than pleiotropic effects for statin-mediated improvement in endothelial function and inflammatory markers in patients with CAD.[68] This review will focus on the beneficial effects of statins during CHD/atherosclerosis and sepsis, conditions both involving vascular inflammation and commonly encountered by anaesthetists and intensivists.

Sepsis

Septic shock is one of the major causes of death in intensive care units and is typified by the presence of bacteria within the circulation. Systemic inflammatory response syndrome may also occur after operation, in about 30–40% of coronary artery bypass patients,[45] but this does not necessitate the presence of bacteria. Sepsis presents with severe and irreversible vasodilatation, hypotension, hypovolaemia, and systemic/tissue inflammation, leading to poor perfusion of tissues, multiple organ failure, and death.

Statins reduce mortality rates from sepsis[2] in both human and animal studies, but compared with CHD, far fewer clinical trials have been undertaken and the majority of these have been retrospective. Patients hospitalized with an acute coronary syndrome, ischaemic stroke, or revascularization and prescribed a statin demonstrated a lower incidence of sepsis compared with controls (71.2 *vs* 88.0 events per 10 000 person-years).[18] A retrospective cohort analysis in 438 patients also determined that statin use before hospital admission, and continued after sepsis, correlated with decreased mortality rates from septicaemia.[34] The DECREASE III trial was designed prospectively to

compare 253 patients given fluvastatin 80 mg and the beta-blocker bisoprolol in 73% of patients, with 247 patients receiving placebo. In the month following major vascular surgery, fluvastatin treatment reduced myocardial ischaemia from 18.9% to 10.9% compared with placebo and reduced the combined endpoint of cardiac death or non-fatal myocardial ischaemia from 10% to 4.8%.[58] However, bisoprolol alone can also decrease cardiovascular complications (DECREASE IV), and therefore, further prospective clinical trials are warranted in the intensive care setting. There are a number of prospective clinical studies of statins and sepsis under way worldwide as described in a previous review.[13] However, these studies have still not reported their findings.

Despite limited prospective clinical data, some studies have been performed in animals with death as the endpoint. In mice, pretreatment with simvastatin for 18 and 3 h before induction of sepsis using the caecal ligation puncture model increased survival rate four-fold.[47] In a subsequent study of treatment with a number of different statins given 6 and 18 h after the onset of sepsis, statins also improved survival[46] (Fig. 2). Indeed, even though survival is not always assessed, it is from animal and laboratory studies that we gain much of our understanding of the endothelial mechanisms by which statins exert some of their pleiotropic effects, which we will now discuss.

Anti-inflammatory actions on vascular endothelium

Atherosclerosis

Atherosclerosis is now known to be more complex than increased lipid deposition on the artery wall due to high LDL levels. LDL also induces endothelial dysfunction, which may be typified by reduced responsiveness to NO-mediated relaxation and exaggerated by shear stress, free radicals, hypertension, and various environmental factors. In addition, the immune response initiates increased vascular smooth muscle proliferation, leucocyte adhesion, and platelet aggregation. These are also important considerations for plaque destabilization and rupture, which has particular relevance for the incidence of coronary events and stokes, but this review will focus on the mechanisms involved in endothelial cell dysfunction, in particular NO, which will be discussed in more detail later.

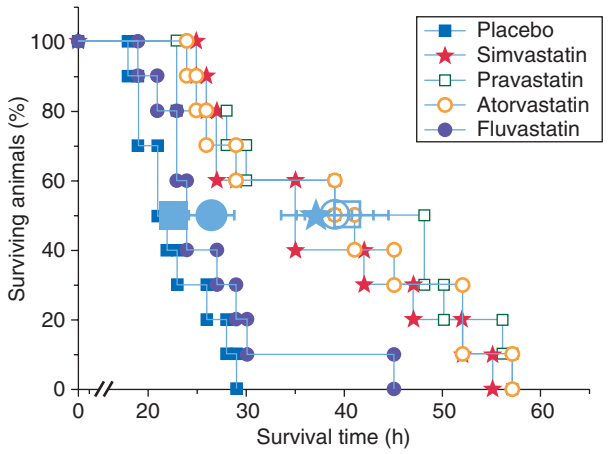

Fig 2 Survival curves and mean survival times after sepsis induction by caecal ligation and puncture. Mean survival time (large blue symbols) of mice treated 6 h after sepsis induction with statins was profoundly increased *vs* that for untreated caecal ligation and puncture mice ($P<0.05$), except for fluvastatin treatment ($P=0.759$). No deaths occurred in sham-operated mice (Merx and colleagues).[46]

Statins and atherosclerosis

Reduced production of NO and increased production of reactive oxygen species, mainly superoxide, is arguably one of the most important mechanisms causing endothelial dysfunction during inflammation. In a homeostatic state, NO is produced from L-arginine via endothelial nitric oxide synthase (eNOS) and is crucial in cardiovascular protection. In atherosclerosis, NO production is inhibited leading to vasoconstriction, inflammation, and thrombotic processes such as leucocyte adhesion and platelet aggregation. Therefore, increasing L-arginine and eNOS during atherosclerosis appears to be beneficial,[28] possibly via the Akt cell survival pathways. Indeed, impairment of the PI3K/Akt/eNOS axis induces detrimental effects on atherogenesis during type-2 diabetes.[39] In atherosclerosis, cerivastatin tended to produce a more pronounced effect on eNOS expression compared with rosuvastatin.[27]

In response to inflammation, cytokines up-regulate inducible NOS (iNOS), which compared with eNOS is generally considered to produce NO in larger quantities. iNOS and isoforms of NADPH oxidase are the major sources of reactive oxygen species in smooth muscle, such as $O^{\bullet 2-}$ and peroxynitrite ($ONOO^-$), which induce tissue damage.[54] The role of iNOS in the development of atherosclerosis is less well established than that of eNOS, although the iNOS inhibitor ONO1714 slows progression of atherosclerosis in rabbits fed a high cholesterol diet.[21] Rabbits placed on an atherogenic diet (0.4% cholesterol) for 6 weeks, followed by an atherogenic diet plus simvastatin (10 mg kg^{-1}) for 2 weeks, also demonstrated reduced cholesterol, VLDL, LDL and HDL, along with decreased expression of iNOS in the aortic arch and carotid artery.[50] iNOS(−/−)/apoE(−/−) mice fed a Western diet containing 42% fat, 0.15% cholesterol, and 19.5% casein also developed significantly smaller advanced lesions than iNOS(+/+)/apoE(−/−) mice.[75] Despite this, inhibition of iNOS alone may not be sufficient to inhibit atherosclerosis, rather therapeutic strategies that increase eNOS and inhibit iNOS may be necessary to achieve this. Indeed, rosuvastatin and cerivastatin prevented cytokine-induced down-regulation in eNOS protein expression in human

umbilical vein endothelial cells, but had no effect on iNOS mRNA expression.[27] Evidence is emerging that different statins may have differential effects on eNOS and iNOS pathways, but this area warrants further investigation.

Drugs that act further down the HMG-CoA reductase pathway also appear to have beneficial effects during atherosclerosis and this is a relatively new area of research. Inhibition of squalene synthesis using lapaquistat treatment for 32 weeks in rabbits decreased plasma cholesterol levels and transformed coronary plaques into fibromuscular plaques.[69] There were concurrent increases in CoQ10 levels and decreased LDL, which correlate with improvement of coronary plaque composition.[69] The squalene synthase inhibitors EP2306 and EP2302 also increased eNOS in cultured bovine aortic endothelial cells and calf pulmonary artery endothelial cells.[73] There is scope for manipulating this pathway therapeutically at points other than HMG-CoA, and there may be advantages in blocking it at a later stage. For example, squalene may have a role in reducing the incidence of some tumours.[71]

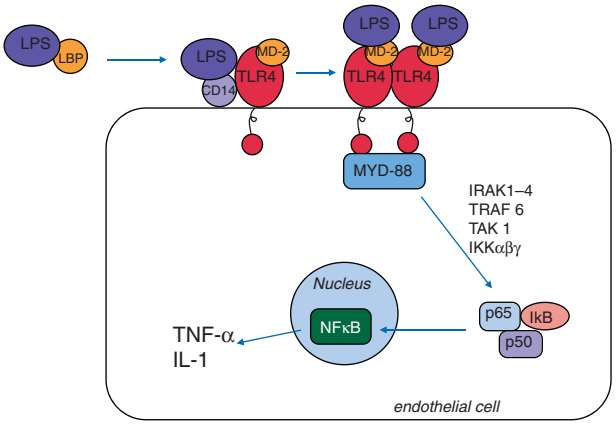

Fig 3 Activation of endothelial cell TLR-4 by LPS. LPS is recognized by TLR-4 at the cell surface through interactions with several extracellular proteins. LBP delivers LPS to CD14. LPS then transfers to MD-2 to form an endotoxin–MD-2 complex which binds and activates TLR-4. Activation of TLR-4 induces a signalling cascade which leads to the activation of the transcription factor NF-κB, mediating the production of pro-inflammatory cytokines including TNF-α and IL-1. Statins may decrease expression of TRL-4.

Sepsis

It is well known that sepsis induces endothelial cell dysfunction. This process contributes to a number of pathophysiological features characterizing this condition, including hypotension, reduced organ perfusion, increased vascular permeability, and increased leucocyte activation, resulting in further release of pro-inflammatory cytokines, free radical release, and tissue damage.[43] To activate the endothelium, bacteria must first act on Toll-like receptors (TLRs). For example, gram-negative lipopolysaccharide (LPS) is recognized by TLR-4 at the cell surface through interactions with several extracellular proteins. LPS binding protein (LBP) delivers LPS to CD14. LPS then transfers to myeloid differentiation protein 2 (MD-2) to form an endotoxin–MD-2 complex which binds and activates TLR-4.[61] TLR-4 induces a signalling cascade resulting in activation of the transcription factor nuclear factor (NF)-κB, in turn mediating the production of pro-inflammatory cytokines such as TNF-α and IL-1 (Fig. 3). The pro-inflammatory cytokines initiated by TLR-4 lead to the release of further pro-inflammatory mediators including NO, for example, anti-TLR-4 mAb reduces the LPS-induced NO from cultured human aortic smooth muscle cells.[24] In a double-blind, placebo-controlled study, 20 healthy volunteers were randomized to receive either simvastatin (80 mg day^{-1}) or placebo for 4 days before i.v. administration of LPS (20 IU kg^{-1}). Simvastatin decreased expression of TLR-4 and TLR-2 on monocytes in response to LPS.[51] Interestingly, in patients with chronic heart failure, TLR-4 expression appears to be higher on monocytes in whole blood, and may therefore regulate inflammation during this disease. Fluvastatin also reduced TLR-4 expression in this same study.[11]

TNF-α and interferon γ (IFNγ), via the transcription factors NF-κB and signal transducer/activator of transcription 1,[78] stimulate overproduction of the calcium-independent iNOS, which is inactive under normal physiological conditions. Up-regulation of iNOS tends to be observed from ∼2 h after the onset of sepsis, and various reports describe it peaking between 2 and 6 h in response to both LPS and caecal ligation puncture, and then being sustained at 48 h.[14 63 67] iNOS then acts to produce large amounts of NO. This high concentration of NO is thought to be both beneficial because it is bactericidal[49] and detrimental because it simultaneously causes vasodilatation and acts as one of the key mediators of inflammation.[16] When there is decreased L-arginine availability (not synthesis), as occurs during sepsis,[32] $O^{\bullet 2-}$ is generated by the uncoupling of NOS, which then reacts with NO to form $ONOO^-$ resulting in tissue damage.[54] Indeed, selective inhibition of iNOS can reduce mortality rates during endotoxaemia in rats.[31]

Initially, eNOS is also increased (up to 2 h), as sepsis modulates the protein Akt that phosphorylates eNOS, leading to Ca^{2+}-independent enzyme activation and increased NO synthesis.[12] The PI3-kinase/Akt pathway is activated by TNF-α and is both anti-necrotic and anti-apoptotic.[81] There may also be abnormalities of the PI3-K/Akt pathway during sepsis that prevent eNOS phosphorylation,[20 42] and again production of peroxynitrite in the face of depleted arginine which is why the role of eNOS is confusing.[54] However, as sepsis progresses (6–48 h), there is limited evidence that eNOS expression decreases, whereas iNOS is increased.[67] Down-regulation of eNOS may be due to activation of caveolin-1 which sequesters eNOS into intracellular stores, thus down-regulating its

activity.[15] As sepsis ensues, there may also be abnormalities of the PI3-K/Akt pathway that prevent eNOS phosphorylation.[20 42] This is important because Akt is generally considered as a protective cell-survival pathway. The mechanisms of eNOS are complex and not fully understood, with function and expression providing different mechanistic information, although sepsis-induced decreases in capillary blood flow impairment may be reversed via an eNOS-dependent mechanism.[74] Taken together, the evidence suggests that the homeostatic balance of iNOS and eNOS alters during the progression of sepsis, contributing to hypotension, multiple organ system failure, and mortality, but complex NO pathways are discussed in greater detail in a recent excellent review article.[54]

In a process similar to that seen in atherosclerosis, restoring this balance may be beneficial during sepsis. This is supported by a caecal ligation puncture study in rats in which administration of arginine, a known precursor of NO, in combination with aminoguanidine, a selective iNOS inhibitor, restored plasma arginine, reduced oxidative stress as measured by expressions of haem oxygenase (HO)-1 and HO-2 in rat liver and lung, and nitrite+nitrate (NO_x) excretion in urine.[80]

Statins and sepsis

There is considerable evidence that statins may activate eNOS, and *in vitro* studies demonstrate that simvastatin and lovastatin increase the half-life of eNOS under low cholesterol conditions[35 36] due to stimulation of PI-3K, thus phosphorylating downstream eNOS and Akt (Fig. 4). For example, rabbits administered fluvastatin demonstrated a 2–2.6-fold increase in eNOS and Akt retrospectively.[42] Simvastatin reduced $O^{\bullet 2-}$ formation during sepsis,[7] which would infer reduced tissue injury, but there is still much research to be undertaken in the field of statins and free radical formation.

Information regarding the effects of statins on iNOS is also limited. Simvastatin has been shown to decrease plasma levels of nitrate *in vivo*, in association with decreased iNOS activity.[16] More recently, chronic administration of simvastatin (10 mg kg^{-1}) has been shown to reduce production of NO via iNOS during inflammation, that is, in response to 4 mg kg^{-1} LPS.[4] Other studies have demonstrated that expression of iNOS in response to TNF-α and IL-1 is also reduced by statins,[40] although endotoxin was not measured directly. In addition, the effects of other statins are not yet known.

Novel NO-releasing statins have been developed, including nitropravastatin (NCX-6550)[60] and nitroatorvastatin (NCX 6560).[48] Nitroatorvastatin led to improved vascular function including an enhanced ability to decrease iNOS expression compared with atorvastatin in LPS-treated macrophages,[48] a finding which indicates that such novel drugs may have beneficial effects on endothelial damage in sepsis and are worthy of further development and investigation.

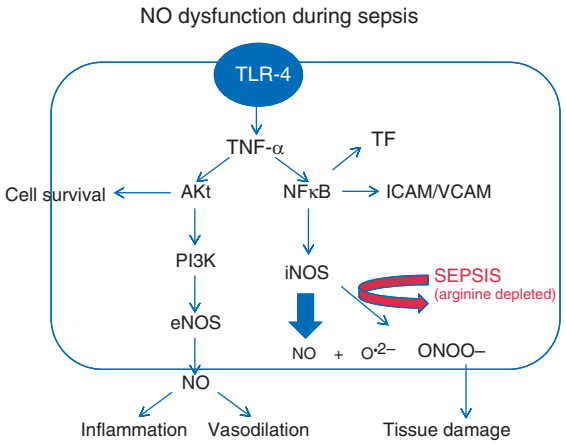

Fig 4 Simplified role of endothelial NO in vascular responses to sepsis. Activation of TLR-4 by LPS results in the up-regulation of cytokines. Both cell survival (Akt) and pro-inflammatory pathways (NFκB) are stimulated. Akt (protein kinase B) may then increase eNOS via G-protein-coupled phosphoinositide 3-kinase (PI3-K), resulting in the release of NO. Likewise NFκB can activate large amounts of NO via iNOS. One tissue damaging pathway occurs when L-arginine is depleted, as occurs during sepsis, when NOS may be uncoupled to produce superoxide ($O^{\bullet 2-}$), which then reacts with NO to form peroxynitrite ($ONOO^-$). NO formed from both eNOS and iNOS can cause tissue damage in this way and cell survival/pro-inflammatory pathways are not mutually exclusive. Peroxynitrite also activates PARP which causes further release of cytokines. The roles of BH4 and NADPH are not shown.

Side-effects

Despite their obvious beneficial effects, as with any drug, statins also induce a number of side-effects that cannot be ignored. The most severe side effects include extreme muscle pain and muscle disease (statin-induced myopathy), along with serious liver problems. Statins also cause a slight increase in the risk of suffering a haemorrhagic stroke.[17]

Statins are used because they inhibit the HMG-CoA reductase pathway and production of cholesterol, now considered as the villain, as it contributes to the development of atherosclerosis and heart disease. Cholesterol, however, is also responsible for regulating cell membrane permeability and fluidity. Furthermore, it is a precursor molecule for synthesis of vitamin D, steroid hormones such as cortisol and aldosterone, along with the sex hormones progesterone, oestrogens, and testosterone (Fig. 1). Statins therefore not only reduce production of cholesterol but may affect other molecules that have a beneficial effect during atherosclerosis and heart disease. Indeed, in a cross-sectional study of 355 men with type-2 diabetes, atorvastatin, but not simvastatin, reduced total testosterone levels (11.4 *vs* 13.4 nmol $litre^{-1}$) compared with no treatment.[72] Testosterone replacement therapy has also been

shown to reduce atherosclerosis and cardiovascular disease in both human and animal studies.[30]

The HMG-CoA reductase pathway results in the production of coenzyme Q10 (ubiquitone) and dolichol. The former is important in maintaining heart strength and muscle function and the latter in the process of cell ageing (Fig. 1). There is some evidence that reduced CoQ10 is induced by statin intake and may explain muscle pain commonly reported with this therapy, as three prospective randomized clinical trials have been performed, with one for and two against CoQ10 replacement therapy reducing muscle pain associated with statin use.[65] A recent study demonstrated improved endothelial NO response in diabetic patients.[19] CoQ10 used in conjunction with statins therefore remains very controversial. We may be reducing cardiovascular disease via cholesterol, but whether we are concurrently increasing the risk of heart disease via inhibition of other by-products from the HMG-CoA reductase pathway is yet to be established.

Possible role in perioperative care

The 2007 American Heart Association (AHA)/ACC guidelines[10] indicate that there is evidence that supports the use of statins perioperatively to prevent cardiac complications during non-cardiac surgery. Considering the pleiotropic mechanisms of statins, and understanding their limitations, we can now consider whether it is appropriate to administer them to patients in order to prevent postoperative complications, particularly re-occurrence of cardiovascular complications after vascular surgery or postoperative sepsis. Evidence is indeed emerging that they may be beneficial, but there is certainly a lack of convincing randomized double-blind prospective clinical trials to support this, particularly with regard to sepsis. We seem to understand more about their anti-inflammatory effects on endothelial cell mechanisms than whether they improve patient outcome. Further to this, more is known about utilizing statins as a prophylactic treatment as opposed to after operation. Limited evidence in the laboratory suggests that statins may be beneficial when administered during sepsis, as 6 h after caecal ligation in mice pravastatin$>$atorvastatin$>$simvastatin, but not fluvastatin, increased survival time from 23 to 37–40 h.[47] This study[47] also highlights that some statins may have more appropriate pleiotropic actions than others, but this has not yet been fully translated to humans. Differential effects may relate to the hydrophobicity of different compounds, with hydrophilic compounds such as pravastatin being more effective. However, again, there is no direct evidence for this and clinical trials are required to compare treatment regimens.

As we discover the pleiotropic potential of statins in settings such as sepsis, the problem arises that many patients presenting for surgery or being admitted to intensive care may already be on statin treatment. Given their potential beneficial effects, we are faced with the situation of withdrawing a potentially beneficial treatment from patients already on statins. Similarly, there are some who would advocate that we should be treating at 'at risk' patients with statins perioperatively.

It is important to try to put this into a clinical perspective. To do this, a number of questions need to be answered.

(1) Do statins provide cardioprotection perioperatively?
(2) Should we put 'at risk' patients on statins perioperatively?
(3) If so, at what dose and for how long?
(4) Should patients on statins continue on them perioperatively?

Do statins provide cardioprotection perioperatively?

There is a reasonable amount of evidence that statins are beneficial. However, most of the evidence is of low quality and comes from retrospective, non-randomized studies. A recent systematic review[23] identified the limited evidence for statins from randomized trials (16 observational studies and only two small randomized trials). In addition, the authors noted serious defects in these studies with regard to control of major variables such as dose, duration of therapy, compliance, drug type, and the inability to show a dose–response relationship. The authors at this time (2006) concluded that there was insufficient evidence to advocate the routine use of statins for perioperative cardiovascular risk reduction.[23] The ACC/AHA guidelines[10] draw a similar conclusion and state that it is unclear how we would identify those patients in whom to initiate statin therapy and for what duration. As stated earlier, prospective randomized studies are under way, but as yet (April 2009) these have not been reported.

Should we put 'at risk' patients on statins perioperatively?

In a prospective randomized controlled trial of 100 vascular surgery patients not previously taking statins, patients were randomly allocated to receive atorvastatin or placebo for 45 days (starting at least 14 days before surgery).[8] There was a 68% reduction (4 *vs* 13) in cardiovascular events in the first 6 months in the atorvastatin group. In cardiac surgery patients, a prospective study of 200 patients randomly allocated to atorvastatin or placebo starting 7 days before operation found a reduced incidence of atrial fibrillation after operation, but no difference in cardiovascular complications overall.[56] A subsequent meta-analysis of six randomized controlled trials with a total of 3557 patients found that statin therapy reduced the risk of new or recurrent atrial fibrillation in cardiac surgery patients.[9] A prospective (non-randomized) study in cardiac surgery patients found statins to be a protective factor for stroke.[1] Meta-analysis of retrospective studies

suggests >30% reduction in mortality.[25] The DECREASE III study allocated 500 patients undergoing major vascular surgery to fluvastatin (80 mg sustained release) or placebo with a measured endpoint of myocardial ischaemia.[58] There was a significant reduction of measured ischaemia in the statin group. However, this study is complicated by the fact that all patients were also receiving bisoprolol. In non-cardiac surgery, retrospective studies suggest benefit, but several prospective studies are due to report soon.

If so, what dose and for how long?

In ACS/MI, 30 days treatment is suggested as the time to produce benefit. There are some suggestions that sustained release formulations may be more beneficial, but this has not been assessed comparatively.[58 66] The vascular surgery study[8] suggests 14 days treatment. There are a number of statins available and a range of drugs, doses, and durations of treatment have been used. However, as noted above,[23] a dose–response relationship has not been shown for any of the drugs in the incidence of perioperative complications.

Should patients taking statins continue them perioperatively?

There is reasonable evidence that patients continuing statins in the perioperative period have 'better' outcomes. There is also some evidence that abrupt stopping of statins is associated with an increased morbidity/mortality[66] as measured by an increase in troponins and cardiac events. The authors also found that sustained release fluvastatin had the best effect. A sequential study of patients undergoing major vascular surgery compared discontinuation and continuation of statins perioperatively. The authors identified statin withdrawal of >4 days as an independent predictor of postoperative myocardial events and suggested that statin therapy should be resumed as soon as possible, preferably within 4 days.[37]

It is our view, therefore, that the only one of these four questions that can be answered with any degree of confidence is the final one—that patients already on statins should be continued on them in the perioperative period. It seems likely that the answer to the questions on cardioprotection and use in 'at risk' patients will be supportive of the use of statins. However, there is a need for high-quality studies to definitively answer these questions. The best drug, dose, and duration of treatment still need to be addressed.

There is a temptation to draw a parallel between statins and beta-adrenergic blockers. In both cases, we are dealing with drugs that are widely used and that appear to have beneficial clinical effects in the perioperative period. However, as can be seen by the long-running debate on beta-blockers, designing and completing appropriate randomized studies to answer these questions is complicated by factors such as the widespread use of the drugs and the multi-factorial nature of processes like sepsis and cardiovascular disease. This issue is further complicated by the possibility of beneficial actions perioperatively of the combination of statins and beta-blockers in patients with cardiovascular disease.[58] This, however, is outside the remit of this review.

It is important that we continue to elucidate mechanisms, such as nitric oxide, involved in any protective effects of statins with careful scientific studies. Similarly, there is a need for well-designed randomized clinical trials to examine the role of statins in perioperative cardioprotection and sepsis. This combination of mechanistic and clinical studies will allow us to make the decision on the use of statins in the perioperative period with an evidence-based rather than empirical judgement.

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