Statins in Intensive Care Medicine: still too early to tell

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Abstract - Patients admitted to an intensive care unit after vascular and cardiothoracic surgery are at very high risk of postoperative cardiac morbidity and mortality. Increasing evidence shows that statins should be prescribed to high risk surgical patients in the perioperative period, and that statin therapy should not be withheld in the postoperative period. Because of their pleiotropic effects, the indication for statin therapy has expanded to other patient categories often admitted to an intensive care unit. There is increasing discussion of a potential role for statins in the management of severe infections, sepsis and renal failure. Therefore statin therapy may be the next logical step in the search for adjuvant therapy in diseases commonly seen on the intensive care unit.

Keywords - Statins, intensive care, sepsis, critically ill

Introduction
HMG-CoA reductase inhibitors (statins) are effective lipid-lowering drugs often used for primary and secondary prevention of cardiovascular disease. However, the overall benefits observed with the use of statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting effects that go beyond cholesterol lowering. Indeed, recent studies indicate that some of the cholesterol-independent or ‘pleiotropic’ effects of statins involve improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response [1,2]. Therefore, the indications for prescribing statins have broadened over the years. The last decade has seen an extraordinary proliferation of evidence that statins decrease mortality in patients who have, or are at risk of developing cardiovascular disease. The benefits of these drugs extend to high-risk patients with normal cholesterol levels and have led some people to suggest that all individuals older than 55 years of age should receive statins as part of a “polypill”.

Methods
We performed a search of the PubMed, EMBASE and Cochrane databases up to July 2010. Review articles, meta-analyses, original papers of clinical trials on the effects of statin therapy were searched combining the following MESH terms: ‘Hydroxymethylglutaryl-CoA Reductase Inhibitors’, ‘Intensive Care’, ‘Perioperative Care’, ‘Sepsis’, ‘Systemic Inflammatory Response Syndrome’ and ‘Critical illness’. Case reports were not included. Language restrictions were not applied. References were searched for other potentially useful articles.

Statins and non-cardiac surgery
Patients are often admitted to an ICU for postoperative care following major (including vascular) surgery. Vascular surgery patients are at very high risk of adverse postoperative cardiac events due to their underlying systemic atherosclerotic disease and high incidence of coronary artery disease. In a study by Landesberg et al., [3] 447 patients, scheduled for different types of vascular surgery, were monitored on the first three postoperative days using continuous 12-lead ECG recording, cardiac troponin T and I and CK/CK-MB measurement. Up to 23.9% of the patients experienced cardiac troponin T or I release, while perioperative ST-segment changes were detected in 14.8% of the patients. Cardiovascular death, defined as death caused by acute myocardial infarction, significant cardiac arrhythmias, congestive heart failure or a death occurring suddenly without explanation, occurred in 27 (1.8%) patients. Myocardial infarction (MI) was diagnosed in 39 (2.6%) of the patients while elevated serum troponin-T levels were present in 354 (24%) of the patients.

Fatal perioperative MI has two potential origins [5,6]. One is a culprit coronary plaque that fissures and ruptures, causing a cascade of thrombogenic events (haemorrhage and
thrombosis) inside the vessel wall, culminating in an MI. Less often, fatal perioperative MI results from long-lasting myocardial ischemia (a demand/supply mismatch of oxygen), typically as a consequence of a fixed coronary stenosis. In nearly half of patients with fatal MI, coronary inflammation is a key contributor. In the perioperative setting, surgical stress induces the release of inflammatory cytokines that disrupt smooth muscle cells in the endothelium and contribute to disruption of a non-obstructing coronary plaque, predisposing to acute thrombus formation.

Retrospective cohort data and data from randomized clinical trials have demonstrated reductions in perioperative cardiac complications with statin use in patients undergoing various types of non-cardiac vascular surgery [7-9]. Recently, the evidence for a beneficial effect of statins has been augmented by DECREASE III [10], a large randomized controlled trial. DECREASE III included nearly 500 statin-naive patients randomized to receive either placebo (n = 247) or fluvastatin (n = 253)-extended release at a dose of 80 mg once daily. One month after surgery, 27 patients in the fluvastatin group (10.9%) had experienced myocardial ischemia, compared with 47 (18.9%) in the placebo group (OR 0.55; 95% CI: 0.34 – 0.88). The number needed to treat to prevent one patient experiencing myocardial ischemia was 12.5. Similarly, the combined secondary endpoint of cardiac death or non-fatal MI occurred in 12 (4.8%) patients of those taking fluvastatin, compared with 25 (10.0%) of those on placebo (OR 0.47; 95% CI: 0.24–0.94).

Cardiothoracic surgery

Over 20 years of experience has accrued with the use of statins in patients undergoing Coronary Artery Bypass Graft Surgery (CABG). The long-term results after CABG are compromised by the progression of atherosclerosis in native coronary arteries and saphenous vein bypass grafts – a process influenced by hyperlipidaemia. Therefore, the role of statins in CABG surgery has been studied intensively. To summarize the data regarding preoperative statin use, Liakopoulos et al. [11] recently performed a meta-analysis of 19 cardiac surgery studies that reported the outcomes of 31,725 patients who were treated with (N = 17,201) or without (N = 14,524) statins before surgery. The authors demonstrated that preoperative statin therapy resulted in a 1.5% absolute risk reduction (2.2 versus 3.7%, statins versus no statins, p < 0.01) and 43% odds reduction for all-cause mortality after surgery (OR: 0.57; 95% CI: 0.49 - 0.67), but not for MI (OR: 1.11; 95% CI: 0.93 - 1.33).

Secondly, it is increasingly recognized that the inflammatory response triggered by on-pump CABG surgery is of clinical importance as it may contribute to the genesis of common postoperative complications and may even exert adverse vascular biological effects on native or grafted coronary vessels. Statins may influence the on-pump inflammatory response, through their pleiotropic effects. Several studies have evaluated the role of statins as anti-inflammatory medications. Dereci et al. [12] showed that pre-operative atorvastatin therapy is effective in reducing the systemic inflammatory reaction associated with CABG and cardiopulmonary bypass by lowering serum high-sensitive CRP and IL-6 concentrations. Chello et al. [13-15] showed that statins reduce neutrophil endothelial-adhesion and increase neutrophil apoptosis, reduce circulating adhesion molecules such as ICAM-1 and E-selectin, improve endothelial function and reduce cytokine release, all by mechanisms that seem unrelated and independent of cholesterol level reduction.

Thirdly, several studies have evaluated the role of statins in the prevention of neurological events after on-pump surgery. After on-pump surgery, the incidence of postoperative stroke is high, ranging from 1.3% to 9.7% [16]. In their meta-analysis, Liakopoulos et al. [11] reported that preoperative statin therapy significantly reduced the risk of stroke after cardiac surgery, with a 0.8% absolute risk reduction (2.1 versus 2.9%, statins versus no statins, p < 0.01) and a 26% odds reduction (OR 0.74; 95% Cl: 0.60 - 0.91) compared to the non-use of statins before surgery. Similarly, statin users show a decreased incidence of postoperative delirium after cardiac surgery as observed in a recent study by Katznelson et al. [17]. Statin use was associated with a decreased incidence of postoperative delirium (OR 0.61; 95% Cl 0.39 - 0.95).

**Timing of preoperative statin therapy**

A major point of discussion is how many days preoperative statin therapy should be started. In the non-operative setting, trials have shown that it takes about 30 days after statin initiation for inflammation levels to minimize, and at least that long for halting of plaque progression to be detected by intravascular ultrasonography [18,19]. In contrast, several studies have demonstrated that high-dose statin loading before percutaneous coronary intervention may improve microvascular coronary perfusion and blood flow within hours [20-22]. There are no data available regarding the timing preoperative, but we prefer to start 30 days before surgery or to postpone surgery if this is an option.

**Renal dysfunction**

Acute renal failure (ARF) is a major problem among ICU patients, with mortality rates around 60% [23]. Despite advances in management strategies, in particular renal replacement therapy, the mortality of ARF in critically ill patients remains high because of coexistent nonrenal organ dysfunction. Although some observational studies have suggested that statin therapy is also associated with improved survival among patients undergoing haemodialysis, an overall benefit of statin therapy in these patients has not been proved [24,25]. Other studies have shown that statin therapy is related to an improvement in renal function. A post hoc analysis of the 'Treating to New Targets (TNT)' trial data suggests that statin treatment may slow or reverse the decline in renal function normally seen over time in patients with stable coronary disease [26]. In the TNT trial, over 10,000 patients with coronary heart disease and LDL cholesterol levels of <130 mg/dl were randomly assigned to double-blind therapy with 10 or 80 mg/d atorvastatin. Mean change from baseline estimated glomerular filtration rate (GFR) showed a progressive increase during the course of the study in both treatment groups. At the end of a 5-year follow-up, mean change from baseline estimated GFR
showed an increase of 3.5 ml/min per 1.73 m² in the 10-mg group and 5.2 ml/min per 1.73 m² in the 80-mg group, which represented increases of 5.6 and 8.3%, respectively. The mechanisms that are involved in this observed nephroprotective effect of atorvastatin have yet to be determined. The observed effect could be linked to the cardiovascular benefits of LDL cholesterol reduction, because on-treatment LDL cholesterol proved to be a significant predictor of change in estimated GFR. However, the pathophysiology of ARF in ICU patients differs from ARF in patients with chronic cardiovascular disease. In the ICU, 35% to 50% of ARF can be attributed to sepsis [27,28]. Postsurgery acute tubular necrosis (ATN) accounts for approximately 20% to 25% of all hospital acquired ARF [29]. Finally, acute radiocontrast nephropathy is the third leading cause of ATN in patients admitted to hospital and up to 7% require transient dialysis or progress to end-stage renal disease [30]. The preventive effects of statins in these patients has recently been demonstrated in a study by Xinwei et al. [31]. They showed that patients taking a higher dose of simvastatin (80 mg vs 20 mg) show a lower incidence of contrast-induced nephropathy after they had undergone a percutaneous coronary intervention (5% versus 14%; p < 0.05). In a retrospective cohort study among 2,760 patients who had undergone cardiac surgery, Huffmyer et al. showed that preoperative statin therapy was associated with a reduction in the need for postoperative renal replacement therapy (OR 0.54; 95% CI 0.38 - 0.77) [32]. Similarly, Welten et al. [33] studied the relation between preoperative statin use and postoperative kidney injury in a group of 2,170 vascular surgery patients. The incidence of kidney injury, defined as >10% decrease in creatinine clearance, was similar among statin users and non-users (29% versus 25%, OR 1.15; 95% CI 0.9 – 1.5). However, if kidney function had deteriorated, statin use was associated with increased odds of complete kidney function recovery (OR 2.0; 95% CI 1.0 – 3.8). To our knowledge, no other studies in humans have shown preventive effects of statins in patients with ARF. All of these effects can be explained by the reversal of (atherosclerotic) kidney injury. The question still remains whether or not statins are also protective in non-atherosclerotic kidney injury. Cholesterol-independent tissue-protective effects of statins are thought to be mediated by their immunomodulatory and anti-inflammatory effects that relate to the ability of statins to block the synthesis of important intermediate products, including the isoprenoids in the mevalonate pathway [34]. The mevalonate pathway mediates the sequential biochemical reactions leading to the synthesis of cholesterol and might be responsible for kidney protection in healthy subjects. In an experimental ischemia-reperfusion model using healthy mice, Sharoy and colleagues demonstrate that pravastatin protected normal mice from renal ischemia-reperfusion injury without any reduction in plasma cholesterol levels [35]. Other studies have shown that in a model of sepsis-induced AKI (i.e. cecal ligation and puncture), pre-treatment with simvastatin improved kidney function, as measured by serum creatinine and blood urea nitrogen [36]. In this study, simvastatin was observed to improve tubular vacuolar degeneration and reverse the increase in vascular permeability, renal microperfusion, and hypoxia seen in this model. Similarly, Sabbatini and colleagues examined whether treatment with atorvastatin could improve the course of ARF after ischemia-reperfusion injury in ageing rats compared with untreated age-matched rats [37]. These investigators showed that the pre-administration of atorvastatin mitigated renal vasoconstriction and restored glomerular filtration values to the baseline by increasing nitric oxide availability and, therefore, improving renal haemodynamics. It can therefore be concluded that statins show protective effects on renal function, regardless of the presence of atherosclerosis.

Sepsis

The hallmark of sepsis syndrome is an intense inflammatory response, which reflects a delicate interaction between the extensive activation of host defence mechanisms and direct and indirect effects of the invading microorganisms and their toxins. As a result, a number of important abnormalities occur during sepsis, including endothelial dysfunction and apoptosis, activation and increased production of cytokines and other pro-inflammatory mediators, activation and extravascular transmigration of leukocytes, and activation of platelets and coagulation and complement systems. To date, activated protein C and low-dose hydrocortisone have emerged as the only inflammation-modulating substances which have been confirmed as beneficial to patients with severe sepsis [38,39]. Consequently, several investigators have evaluated the role of statins in the prevention and treatment of sepsis. Clinical studies that have described effects of statins in sepsis have either addressed the effects of statins in reducing sepsis incidence and severity or retrospectively looked at mortality in those taking statins who developed sepsis. Although the exact mechanisms behind the observed beneficial effects of statins in septic patients are still unknown, several factors could be involved, including the immunomodulatory and anti-inflammatory effect of statins and their impact on endothelial function. Several clinical studies have shown the beneficial effect of statins on clinical outcome [40-42]. In a small prospective observational study, Almog et al. have shown that patients who were treated with statins before the occurrence of a bacterial infection had a reduced rate of severe sepsis (rate ratio 0.07 (95% CI 0.01 – 0.51) and ICU admission [40]. More recently, Christensen et al. have shown that preadmission use of statins was associated with reduced risk of death within 30 days and one year in general ICU patients [43]. In a recent meta analysis by Teyjeh et al., an improvement in the chance of 30-day survival in favour of patients on statin therapy (treatment cohorts) was found compared to those patients not on statins (OR 0.55; 95% CI 0.36 - 0.83). The same beneficial effect was found in the prevention cohorts (OR 0.57; 95% CI 0.43 - 0.75) [44]. The overall conclusion is that there is circumstantial evidence from retrospective database enquiries and observational studies that statins may be helpful in the treatment of sepsis. However, properly conducted, randomized, placebo-controlled trials in the context of sepsis and septic shock are still lacking. Currently several such trials are under way or will soon be ready to include patients [45].
Neurovascular diseases
Traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH) remain one of the leading causes of mortality and morbidity worldwide in individuals under the age of 50 years. Despite extensive efforts to develop neuroprotective therapies for these conditions, there has been little successful outcome in any trial of neuroprotection to date. So far, nimodipine is the only drug that decreases the incidence of vasospasm and poor outcome after SAH [46]. One suggested therapeutic option is treatment with statins. Several earlier conducted randomized controlled studies have shown that acute initiation of statin treatment directly after aneurysmal SAH decreased the incidence of radiological vasospasm and clinical signs of delayed cerebral ischemia [47,48]. However, a recent meta-analysis by Vergouwen et al. could not detect a statistically significant reduction in delayed cerebral ischaemia (pooled risk ratio 0.57; 95% CI 0.29 - 1.13), vasospasm (pooled risk ratio 0.99; 95% CI 0.66 - 1.48), poor outcome (pooled risk ratio 0.92; 95% CI 0.68 - 1.24) and mortality (pooled risk ratio 0.37; 95% CI 0.13 - 1.10) [49]. Unfortunately, all studies to date have been conducted with only small sample sizes. A large-scale Phase III study is presently being conducted to investigate the effect of statins in aneurysmal SAH (www.stashtrial.com), but the results are not expected for some time.

Several studies in animals have evaluated the role of statins in TBI [50,51]. In a study by Chen et al., the pre-administration of lovastatin to rats subjected to TBI was shown to improve functional outcomes and reduce the extent of brain damage, with a concomitant decrease in tissue levels of TNF-α and IL-1β mRNA and protein [50]. So far, there are no data available about the role of statins in TBI in humans. Results from recently started clinical phase II trials can be expected in the next few years.

Safety issues
A major concern of administering statins to patients in the ICU is that patients who undergo major vascular surgery are often not able to take oral medications shortly after surgery, for example, because of postoperative paralytic ileus. Since there is no intravenous formula for statins, the interruption of statin therapy in the immediate postoperative period is a serious concern, especially because it is known that these vascular surgical patients are at the highest risk for adverse cardiac events in the first 3 days following surgery. A study by Schouten et al. [52] showed that acute statin withdrawal in the perioperative period is associated with an increased risk for perioperative cardiac events compared with statin continuation in long-term users. Patients unable to take statins postoperatively had more than a 7-fold increased risk of nonfatal myocardial infarction and cardiac death. More importantly, the study showed that the extended-release formula of fluvastatin was superior compared to other statins used by patients who discontinued statin therapy. There are several possible explanations for these observations. Fluvastatin is the only statin with an extended-release formula. Because most patients with statin withdrawal restarted statin therapy < 3 to 4 days after surgery, it might be hypothesized that the extended-release fluvastatin formula is capable of extending the duration of the pleiotropic effects of statins. Furthermore, the pharmacokinetics of statins might be influenced by concomitant drug use in the perioperative period. Of special interest in this respect is the cytochrome P450 (CYP) isoenzyme system. Most drugs are metabolized in the liver by the CYP 3A4 isoenzyme. As a consequence, this might cause interaction with simvastatin and atorvastatin, which are also metabolized by this pathway [53]. Fluvastatin, in contrast, has only limited interactions with the CYP 3A4 pathway, because it is mainly metabolized by the CYP 2C9 isoenzyme. As shown in a review by Bellosta et al., other differences between statins include half-life, systemic exposure, maximum plasma concentration, bioavailability, protein binding, lipophilicity, the presence of active metabolites, and excretion routes [54]. Fluvastatin is the only statin that is a racemic compound, half of the molecule being presumably inactive at reducing plasma cholesterol. It is not excluded that some of the beneficial pleiotropic effects may be shared by the “nonactive” half, therefore potentially increasing that capacity. Side effects of statins include elevations in creatine kinase, myopathy, back pain, and arthropathy. Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with fluvastatin and other HMG-CoA reductase inhibitors as well.

Safety of statins in the ICU setting
As previously mentioned, rhabdomyolysis and myopathy can be devastating side effects in combination with statin use. In the intensive care setting of prolonged sedation, clinical monitoring may not always be possible and important and dangerous side effects or drug interactions may go unnoticed. There are several known interactions between statins and other drugs that are metabolized by, or are of influence on CYP3A4. Drugs that inhibit this isoenzyme are antifungals, erythromycin and other macrolides, histamine-2 blockers, cyclosporine, calcium channel blockers and grapefruit juice. All these agents lead to an increase in plasma concentration of statins and the use of pravastatin or fluvastatin may be preferable since these are not primarily metabolized by CYP3A4 [55-57]. Rifampicin, phenobarbital, carbamazepine and phenytoin are examples of drugs that induce both CYP3A4 and CYP2C9 and therefore lead to increased metabolism of hepatically metabolized statins. The lipid-lowering effect of statins can be reduced by concomitant use of these drugs. Warfarin is metabolized by CYP3A4 and CYP2C9, and there have been few reports indicating that patients on statins and warfarin are potentially at risk for bleeding complications. Careful monitoring of the International Normalized Ratio (INR) is advised in patients on warfarin, following the start of or any change to statin use (except pravastatin) [58,59]. Commonly used agents for sedation may have interactions with statin therapy as well. Midazolam, commonly used for sedation in ICU patients, is metabolized in part by the same CYP isoenzyme as most statins, CYP3A4. In theory this could lead to interactions and alterations on the efficacy of one or both drug. However, a recent report showed that statins had no influence on midazolam pharmacokinetics in healthy subjects, thus dismissing this theory [60]. Therefore, the incidence of side effects depends on the type...
of statin used. For lovastatin, simvastatin, and atorvastatin, which are metabolized by CYP 3A4, an incidence of 0.73 cases/million prescriptions has been reported. For pravastatin and fluvastatin which are not oxidized by the cytochrome P 450 system, the rate is 0.15/million prescriptions [55].

**Discussion**
Statins have become a cornerstone in the treatment of patients with atherosclerotic disease, since their use has resulted in improvements in outcome. Current evidence also shows that statins decrease perioperative morbidity and mortality in patients undergoing (non-cardiac) vascular and cardiothoracic surgery. However, a sudden discontinuation of statin therapy in the postoperative period appears to lead to a rapid loss of its vascular protective effects, and, in some instances, vascular deleterious and prothrombotic activity may increase above baseline levels leading to adverse effects. Beyond their lipid-lowering properties, statins have pleiotropic properties that may modulate the inflammatory cascade and could potentially be useful in the management of inflammatory conditions such as acute renal failure, neurovascular diseases and sepsis. Several studies have demonstrated beneficial effects of prior use of statins in the development and the progression of these diseases and there is evidence to support the fact that the use of statins may be associated with a decreased hospital mortality caused by the above disorders. It should be underlined, however, that these data come mainly from observational retrospective investigations and randomized prospective studies are warranted to confirm these encouraging results. Finally, it should be noted that statins are infrequently associated with adverse events and are generally safe and well tolerated. However, in the ICU setting, the critically ill patients treated on intensive care units certainly represent a population at increased risk and should thus be monitored closely for signs of adverse effects. Future trials will give us more insight into the known and possible unexpected side effects.

**Conclusion**
Perioperative statin therapy reduces postoperative myocardial infarction and mortality after cardio and/or vascular surgery. The available evidence suggests that patients on statin therapy should not discontinue their statin intake in the postoperative (intensive care) period. Indications where statin therapy might be indicated in the near future are expanding, but the evidence is still not strong enough to justify a generalised use of statins in the intensive care setting. At this point in time, the risk of potential side effects and drug interactions outweigh the possible benefits associated with statins. We do not therefore recommend the liberal use of statins in the ICU setting. If there is an indication for statin therapy, pravastatin and fluvastatin seem to have the highest safety profile and should be first choice in the ICU.

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