

Statins in Critical Care

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Introduction

The role of statin drugs in the reduction of serum lipids has been well documented.¹⁻³ More recently we have evidences which suggest that statins may positively impact many organ systems and disease states independent of lipid reduction. These have added a wide scope of potential targets for statin therapy ranging from plaque stabilization in acute coronary syndrome (ACS) to decreasing loss of renal function; lowering mortality in patients with diastolic heart failure; to prevention and treatment of stroke. This review summarizes the evidence in favor of role of statins in intensive care unit and briefly discuss the role of statins in prevention and treatment of sepsis as a potential future application of statins in critical care (see Table 1).

Statins in Acute coronary syndromes

While the benefit of statin therapy in patients with stable coronary artery disease is clearly

Table 1 : Potential use of statins in critical care

Acute coronary syndrome
Percutaneous coronary intervention
Septicemia
Cerebro-vascular accident
Heart failure
Post organ transplant
Perioperative in non cardiac surgery

recognized,^{1,3} the positive impact of the initiation of statin therapy immediately following ACS occurrence has emerged only recently. Both STEMI and NSTEMI frequently require intensive-care treatment and these patients are at high risk for recurrent coronary events, sudden death and all-cause mortality. The stabilization of vulnerable lesions is a critical aspect in preventing these events following ACS. Despite significant advances in antiplatelet and antithrombotic therapy, these therapeutic options alone do not appear to suffice in treating the unstable plaque stabilization. Through their cholesterol lowering and pleiotropic effects, statins are viewed as important contributors to plaque stabilization.⁴ Besides this statins have several other benefits in patients of ACS which are highlighted in Table 2.

A number of retrospective and observational studies have suggested that initiating statin therapy immediately after an ACS is associated with

Table 2 : Rationale for use of statins in ACS

Statins cause stabilization of vulnerable plaque
Decrease mortality in ACS patients
Decrease MACE in patients undergoing PCI
Antiarrhythmic action
In hospital administration improves compliance
Sudden withdrawal of statins during an ACS can be hazardous

significantly reduced rates of recurrent coronary events and death.⁵⁻¹¹ These have been followed up on by large-scale, randomized, controlled trials. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL)¹² trial was the first to demonstrate a reduced rate of recurrent cardiac events by statin therapy. In this study 3086 patients with unstable angina or non-Q-wave infarction were randomized within 24–96 h after hospital admission to receive either 80 mg of atorvastatin or placebo in addition to state-of-the-art therapy for 4 months after ACS. The primary endpoint of the trial – death, cardiac arrest, myocardial infarction or worsening unstable angina requiring emergency hospitalization at 16 weeks – showed a relative risk reduction of 16% [95% confidence interval (CI), 0–30; P = 0.048; absolute risk reduction, 2.6%].

These findings were supported and extended by the Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE IT)¹³ This trial randomized 4162 patients hospitalized for an ACS (NSTEMI, and STEMI). Patients were included within 10 days of their index event, and were randomized to either pravastatin (40 mg daily), or atorvastatin (80 mg daily). Of note, this study also included a significant number of patients (69%) post percutaneous revascularization. Results showed a strong trend toward benefits in the primary endpoint (death from any cause or a major cardiovascular event) in the high-dose atorvastatin group within 30 days. A statistically significant decrease in the primary endpoint arose at 180 days (relative risk reduction of 16% (P value=0.005; absolute risk reduction, 3.9%). The secondary endpoints (revascularization, unstable angina requiring hospitalization, and the combined endpoint of MI, revascularization, or death from coronary heart disease) also showed a significant decrease during the overall 2-year assessment period. The benefit, derived from intensive versus conventional lipid-lowering therapy arose on top of background evidence-based ACS therapy (including antiplatelet therapy, β -blockers and angiotensin-converting-enzyme inhibitors in a large majority of patients).

In contrast, the Aggrastat to Zocor (A to Z)¹⁴ trial did not demonstrate superiority for the intensive statin regimen ($p = 0.14$). A statin trial failing to achieve a statistical significance was a major setback. But when this trial was critically analyzed it was found that the CRP level reduction was only 17% in this trial as compared to 34% and 38% in the MIRACL and PROVE-IT trial. More than the lipid level it is the anti-inflammatory action of statins which is more important in ACS. Secondly the benefit was not seen in the first three months in the trial but seen thereafter. This could be due to the fact that statin was titrated to its maximum dose only after 3 months.

Based on the findings from these three large randomized trials it has been speculated that the early benefits of statin therapy may be caused largely by anti-inflammatory effects, whereas the delayed benefits are more likely to be lipid-modulated.

In hospital administration of statin improves long term compliance.

It has also been seen that in hospital administration of statin improves long term compliance. Patients will be more likely to understand the importance of lipid lowering therapy if statin is started during hospitalization for ACS and then he is less likely to discontinue the therapy. The CHAMP programme addressed this issue in the pre-discharge cardiac patient.¹⁵ They found that the 1 year compliance rate increase from 10% to 91% when statins were prescribed during hospitalization for ACS than when it is prescribed on out patient basis.

Taken together, the evidence suggests that, in the absence of contraindications or intolerance, statin therapy should be initiated within 24-96 h after an ACS regardless of pretreatment cholesterol levels. In addition, experimental and clinical findings support pleiotropic statin effects contributing to plaque stabilization and improved endothelial function. Early initiation of high-dose statin therapy will likely maximize clinical benefit derived from both aggressive LDL-cholesterol lowering and pleiotropic effects. Until the efficacy and safety

Table 3 : Randomized trials of statins in critical care

S No	Trial	n	Subsets	Statin	Follow up	Result
1	MIRACL ¹²	3086	ACS (NSTEMI)	Atorva-Statin (80mg)	16 Weeks	16% RR in composite end point of death MI & TVR (P=0.48)
2	PROVE IT-TIMI 22 ¹³	4162	ACS (NSTEMI & STEMI)	Atorva-Statin (80mg)	2 Years	16% RR in all cause mortality (p=0.005)
3	A TO Z ¹⁴	4497	ACS (NSTEMI)	Simva-Statin (40mg BD)	2 Year	Non significant trend (p-0.14) in favour of high dose simvastatin
4	ARMYDA-ACS ¹⁷	191	PCI for NSTEMI	Atorva-Statin (80mg)	30 Days	Significant reduction of composite end point of death MI & TVR (P=0.01)
5	SPARCL ⁴²	4731	Recent stroke/TIA	Atorva-Statin (80mg)	4.9 Year	Decrease recurrent stroke by 16% (p=0.03)

of other statins have been proven in this context, atorvastatin 80 mg should be used as the most firmly established statin for this purpose. Table 3 summarizes the randomized trials of statin in critical care.

Statin withdrawal syndrome

The possibility of a detrimental rebound effect from statin withdrawal has been proposed by Heeschen et al.¹⁶ Among acute coronary syndrome subjects, in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study, statin therapy was associated with a reduced event rate at 30-day follow-up compared with patients without statins (adjusted RR 0.49, P = 0.004). However, if statins were discontinued after admission, cardiac risk tended to be higher compared to those who never received statins (RR 1.69, P = 0.15). Continuation of statin therapy was one of the independent predictors of patient outcomes. Therefore stopping statins in an ACS patient who was already on statins could be dangerous.

Statins and percutaneous coronary intervention in ACS

The pleiotropic effects of statins are also being studied for their effects following PCI in acute coronary syndrome. The Atorvastatin for Reduction of Myocardial Damage During Angioplasty-Acute Coronary Syndromes (ARMYDA-ACS) trial

demonstrated that short-term pretreatment with atorvastatin 80 mg reduces the incidence of cardiac events in ACS patients undergoing early PCI, a benefit largely driven by a significant reduction in post procedural MI.¹⁷ This trial randomized 171 patients with non-ST-segment-elevation ACS to pretreatment with atorvastatin (80 mg 12 hours before, and 40 mg immediately prior to PCI) or to placebo. All patients were given a 600-mg loading dose of clopidogrel and long-term atorvastatin treatment (40 mg/day). The primary endpoint, a composite of death, MI, and TVR at 30 days, was significantly lower among ACS patients pretreated with atorvastatin compared with those treated with placebo (5% vs. 17% respectively, P = .01). The incidence of MACE was primarily driven by significant differences in post procedural MI, with reductions in creatine kinase-MB (CK-MB) and troponin levels in patients pretreated with atorvastatin. In multivariate analysis, pretreatment with atorvastatin was associated with an 88% reduction in the relative risk of MACE at 30 days. If confirmed by larger randomized trials, this study may support the indication for “upstream” administration of high-dose statins in patients with ACS undergoing an early invasive strategy. Future studies in larger populations will need to determine if these peri-procedural reductions in MI translate into clinically meaningful reductions in hard events.

Table 4 : Summary of human observation studies in sepsis

Study design	Setting	(n)	Study effect
Retrospective cohort ²⁷	Elderly patients with cardio-vascular disease hospitalized for sepsis	69168	Decrease sepsis & mortality
Prospective cohort ²⁸	Patients admitted to hospital with suspected or confirmed bacterial infection	361	Decrease sepsis & need for intensive care admission
Retrospective cohort ²⁹	Patients admitted to hospital with bacteremia	388	Decrease mortality in statin treated patients
Retrospective cohort ³⁰	Patients with discharge diagnosis of pneumonia	787	Decrease 30 day mortality
Retrospective cohort ³¹	Intensive care patients ventilated more than 96 hours	438	Increase mortality
Retrospective cohort ³²	Patients requiring hospital admission for bacteremia	438	Decrease mortality with pre-treatment and when treatment continued after diagnosis

Statins and Sepsis

Background

Current prescribing guidelines recommend that statin therapy be discontinued in patients with an acute illness such as severe infection and septicemia. This is based on the assumptions that serum lipoproteins may protect against the lethal effects of endotoxemia by binding and inactivating endotoxin.¹⁸⁻²¹ Furthermore, a low serum cholesterol concentration is an independent predictor of infectious complications and mortality in hospitalized patients.^{22,23} But recently, enormous data supporting the favorable role of statins in both prevention and as adjuvant therapy in the treatment of septicemia has piled up. This would challenge the current prescribing guidelines to with-hold statins in acutely ill patients and warrants further prospective investigation.

Mechanism of benefit of statins in septicemia

Possible mechanisms include interference with leukocyte–endothelium interaction, prevention of toxin-induced cellular damage and modulation of endothelial function.

Leukocyte–endothelial interaction is a critical event that precedes the trans-migration of leukocytes from the vasculature to tissue.²⁴ Statins interfere with many of the steps involved in this process by increasing the level of endothelial NO, inhibiting the adhesion of monocytes to the endothelium and

by inhibiting the release of polymorphonuclear (PMN) cell chemoattractants.

Statins also exert activity against a toxin released by *Staphylococcus aureus* in septic patients. Elevation of HDL by statins play a role in neutralisation of endotoxins in sepsis.

Statins deplete isoprenoids, which are important non-sterol cholesterol precursors. These precursors are essential for the farnesylation and geranylation of membranal G proteins, which play an important role in the signal transduction pathways that determines cellular migration and proliferation.²⁵

Improvement in Vascular Function in sepsis is also reported by statin use.²⁶ Endothelial cells play an important role in the control of vascular tone, permeability, blood flow, coagulation, thrombolysis, inflammation, tissue repair, and growth. Endothelial activation, dysfunction, and apoptosis play a crucial role in the pathogenesis of sepsis and subsequent multiple organ dysfunction. It has been shown that statins increase expression and enhance activity of endothelial NOS, upregulate prostacyclin and tissue – type plasminogen activator, and downregulate tissue factor, endothelin – 1, and plasminogen activator or inhibitor – 1 (PAI – 1) thus improving endothelial functions.

Evidences from Observational data

No data from randomised trials of statins and sepsis are available, but observational studies lend

support to a potentially important preventive and/or treatment effect (Table 4). The largest study to date is a population-based cohort study involving the linked administrative databases in Ontario, Canada, and included a matched cohort of 69168 patients. The incidence of sepsis was substantially lower among patients receiving statins (hazard ratio [HR] 0.81; 95% CI 0.72–0.91). The protective association between statins and sepsis persisted in high-risk subgroups including patients with diabetes mellitus, malignancy, and those receiving oral steroids. Significant reduction in severe sepsis (HR 0.83; 95% CI 0.70–0.97) and fatal sepsis (HR 0.75; 95% CI 0.61–0.93) were also observed.

Due to their observational nature, the studies presented above may suffer from selection bias and hidden confounding, and we should interpret these results with caution. Taken together, however, these early data suggest that statins may, in human beings, contribute to preventing sepsis and have a role in the treatment of sepsis.

Thus there is growing interest among clinicians in the role that statins may play in preventing and treating serious infections. If such an effect of statins can be supported by randomized controlled clinical trials, then the implications could be far reaching. The stage is now set for randomized clinical trials that will determine the precise role, if any, that statins may have in preventing and treating sepsis.

Statins and Stroke

Statin therapy has been shown to significantly lower the risk of stroke in several studies in patients with coronary heart disease.^{1,33,34} Whether statins prevent strokes in patients without heart disease is currently under evaluation in several trials. Because cholesterol is often not elevated in stroke patients³⁵ the benefit of statins in stroke patients may be an effect independent of cholesterol lowering such as stabilization of pre-cerebral atheroma in the aorta and carotid arteries³⁶ and the inhibition of platelet reactivity.³⁷ Furthermore, some of the beneficial CNS effects of statins may be due to their

augmentation of NO production (NO may improve CNS collateral blood flow), enhance cerebral vasodilator responses and prevent apoptosis.^{38,39} For example, in a murine model of ischemic stroke, both atorvastatin and simvastatin increased cerebral blood flow and decreased infarct size in wild-type but not in an eNOS-knockout mice.⁴⁰ Pravastatin was compared to placebo in patients with subarachnoid hemorrhage and it was found that those randomized to pravastatin had a 61% reduction in the incidence of ipsilateral vasospasm and an 82% reduction in the incidence of delayed ischemic deficits.⁴¹

The recent clinical trial, SPARCL was the first randomized study which showed that statins prevent recurrent stroke and transient ischemic attack in patients who have already had 1 of these events.⁴² We already knew they prevented strokes in patients with coronary disease, but this is the first time it has been looked at in patients with cerebrovascular disease. Therefore, statins should get the attention of neurologists for use in these patients.

Statins in Heart Failure

It was traditionally believed that statins may be detrimental in the treatment of heart failure because they lower the lipid pool. It was thought that a large lipid pool absorbed the cytokines which are harmful in heart failure. Data from trials in the last two years show that this concept is changing. In fact statins improve microvascular circulation and endothelial function by stimulating angiogenesis and modulating the synthesis and activity of endothelial nitric oxide synthase and endothelin-1. In animal models, statins impact the process of cardiac remodeling by reducing ventricular hypertrophy in response to angiotensin II, and through down regulation of angiotensin I receptor expression and reduction in the secretion of matrix metalloproteases. In HPS study there were hardly any heart failure related deaths in patients on simvastatin. In a study of elderly population with heart failure, Roy et al showed survival benefit with

Table 5 : Concerns in using statins in ACS

Myositis & rhabdomyolysis with high doses
 Safety in patients with LDL < 70 mg%
 Clopidogrel statin drug interaction
 Post MI Lipid profile measurement
 Acute care priority- time & economic constraints

statins over standard therapy.⁴³ Analysis of PROVE IT TIMI 22 trial showed reduction of heart failure hospital admissions. Sole et al showed an increase in LVEF in patients with non ischemic dilated cardiomyopathy.⁴⁴ Survival benefit has been shown with statins in diastolic heart failure in a study by Fukata et al.⁴⁵ Meta analysis of PROVE IT, A to Z, TNT and IDEAL study showed a 27% reduction of heart failure admission rates with statins compared to placebo.

Benefit of statins in patients with ischemic heart disease and dyslipidemia is proved beyond doubt. So such patients with heart failure would anyway be on statins. With the available data, non ischemic patients of heart failure also seem to benefit with statins. Further studies would be needed before a confident guidelines be drawn in this regard. Three large ongoing randomized clinical trials should help to settle the debate over the safety and efficacy of statin therapy in patients with HF: the GISSI-HF⁴⁶, CORONA, and UNIVERSE trials.

Statins in Organ Transplantation

Statin use is associated with improved function and survival of lung transplantation. Following allograft lung transplantation, statin recipients had a lower incidence of acute rejection and obliterative bronchiolitis. The 5 year survival rate was better compared to placebo.

A meta-analysis of statins and survival in de novo cardiac transplantation has also reduced one-year mortality for heart transplant recipients.⁴⁷ Although the mechanism for these benefits is not clear, it is likely to be an immunomodulatory effect of statins.

Peri-operative application of statins

Adverse peri-operative cardiac events are an important source of hospital morbidity and mortality. Among patients undergoing major non-cardiac surgery, the overall incidence of peri-operative myocardial infarction is 2–3%, and within high-risk populations, such as those undergoing vascular surgery, rates as high as 34% have been reported.⁴⁸ Several retrospective trials^{49,50} have suggested a beneficial role for statins in surgical patients with the number needed to treat (NNT) ranging from 3 to 103.⁵¹ In two prospective studies, patients subjected to vascular surgery were studied with a clear benefit demonstrated for statin therapy.^{52,53} Of note, none of the studies found an increased incidence of adverse effects related to statin therapy. Thus patients undergoing vascular surgery, representing a population at high risk for cardiac complications, should receive statin therapy. The optimal therapeutic regime with respect to dose and duration of pre-operative and post-operative treatment remains to be determined by further prospective studies as well as the potential benefit for surgical patients with lower cardiovascular risk.

It is important to stress that all patients in whom long term statin therapy is indicated per se should continue their therapy post-operatively, and care should be taken that statin therapy is not unintentionally withdrawn in the peri-operative period.

Cautions: There may be several concerns when using high dose statins in critically ill patients as shown in Table 5.

High dose statin therapy are known to alter liver function and cause myopathy, although they are rare in large studies with an overall rates of 0.6% for serious musculoskeletal and 1.3% for hepatic toxicity.⁵⁴ In order to optimize patient outcomes, clinicians should be aware of specific patient characteristics, such as advancing age, gender, body mass index, or glomerular filtration rate, which predict muscle and hepatic statin toxicity. In

Table 6 : Recommendations From the National Lipid Association Statin Safety Task Force for Muscle Issues

For Patients With Muscle Symptoms and/or an Asymptomatic CK Elevation or Both

1. First, rule out other etiologies (including increased physical activity, trauma, falls, accidents seizure, hypothyroidism, infections, alcohol or drug abuse, and rheumatologic or other muscle disorders).
2. CK monitoring
 - a. Obtain CK for unexplained muscle symptoms
 - b. May obtain baseline CK in high-risk patients, optional for others
 - c. No need to routinely monitor CK levels during therapy
3. Discontinue the statin if intolerable muscle symptoms occur, with or without CK increase
 - a. Rechallenge with same or lower dose of same or different statin once symptoms resolve
4. If tolerable muscle symptoms with CK < 10x ULN, continue statin at same or lower dose until symptoms dictate otherwise
5. Discontinue the statin and reconsider risk/benefit if:
 - a. CK > 10x ULN even with tolerable muscle symptoms
 - b. CK > 10,000 IU/l
 - c. Worsening serum creatinine and/or need for intravenous hydration therapy

a critically ill patient with multi organ dysfunction and patient exposed to multiple drugs, especially many of which would be metabolized by CYP 450, one has to be very cautious. Regular monitoring of CPK and Liver enzymes are mandatory in such patients. The national lipid association has issued some recommendations for patients with muscle symptoms and /or raised CPK levels which are highlighted in Table 6.

Is LDL below 70 mg% safe? or unphysiological? There should not be any serious concern about dropping LDL cholesterol levels too low, because cholesterol delivery to peripheral tissues such as the adrenal gland occurs mainly via HDL. At birth, our LDL is 40 mg/dl. In utero the LDL is 25 mg/dl. Normal LDL-C range is 50-70 mg/dl for healthy human neonates, native hunter gatherers, free living primates and other wild mammals who do not develop

Table 7 : Unanswered issues with statins in critical care

How long should we give statins after ACS

Can 10 mg dose give the same benefit as 80 mg

Is it useful in patients with baseline LDL < 70 mg%

Are all statins same in respect to their pleiotropic effect

atherosclerosis. In PROVE IT - TIMI 22 substudy 91% of patients had LDL < 100 mg% at the end of 4 month and there was no significant differences in safety parameters including muscle, liver, retinal changes, I.C. hemorrhage or death.⁵⁵ Groups with LDL < 40 & 40-60 had fewer major CV events. Therefore there is no reason to fear very low LDL. Infact aggressive LDL lowering results in incremental benefits without additional safety concerns.

Is there any clopidogrel- statin drug interaction? Since most of the patients with ACS are also on clopidogrel, another concern with using statins in acute coronary syndrome may be a fear of clopidogrel-statin drug interaction.⁵⁶ The current consensus regarding this issue is that although interaction between CYP3A450 metabolized statin is theoretically possible but there is insufficient convincing data to judge the clinical consequences of this interaction.^{57,58} Landmark clinical trials still promote the concomitant use of statins and clopidogrel.

Unanswered issues: In spite of ample of evidences, still there are many unanswered issues with statins in critical care (Table 7).

Conclusion

Statin therapy should be continued in ICU patients in whom it is warranted due to underlying cardiovascular disease or risk factors. In ACSs, statin therapy should be initiated within 24–96 h regardless of pretreatment cholesterol levels. Statins have been found to reduce the recurrence of stroke. Patients undergoing vascular surgery should receive peri-operative statin therapy. However placebo controlled clinical trials are required to further consolidate the experimental and observational evidence for prevention and treatment of sepsis.

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