medicina *intensiva*

REVIEW

Effect of the administration of statins in non-cardiac critical disease

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Abstract   Administration of statins has been shown to be effective in reducing cardiovascular mortality. Their benefit could expand towards other areas of intensive medicine, it being possible to decrease mortality of the critically ill patient. There are several studies, although without a high level of evidence, that have detected a possible benefit when they are administered as well as clinical deterioration when they are discontinued, compared to those patients who had previously taken them.

Even though most of the patients who had previously taken statins did so as primary or secondary prevention, thus having greater comorbidity, overall, a decrease is detected in the mortality of these subgroups. This benefit could be generalized to all the critical conditions, although studies with a higher level of evidence are needed for their adequate comparison.

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Efecto de la administración de las estatinas en la patología crítica no cardiológica

Resumen   La administración de estatinas se ha mostrado eficaz en reducir la mortalidad cardiovascular. Su beneficio podría expandirse hacia otras áreas de la medicina intensiva, pudiendo disminuir la mortalidad del paciente críticamente enfermo. Existen diversos estudios, aunque sin un alto nivel de evidencia, en el que parece detectarse un posible beneficio en su administración, y un empeoramiento clínico con la discontinuación de estos fármacos, sobre los pacientes que previamente las tomaban.

A pesar de que la mayoría de los pacientes que tomaban previamente estatinas lo hacían como prevención primaria o secundaria, teniendo por tanto una mayor comorbilidad, en global se detecta una disminución de la mortalidad en dichos subgrupos. Este beneficio podría ser generalizado ante toda la patología crítica, aunque se requieren estudios con un mayor nivel de evidencia, para su adecuada contrastación.

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Introduction

In Intensive Care Medicine there is evidence that patients with critical disease of any origin can develop potentially reversible myocardial dysfunction capable of modifying the prognosis[1] ([Figure 1], [Figure 2] and [Figure 3]). Such myocardial dysfunction in critical patients is similar to stress myocardiopathy and is of uncertain etiology – though
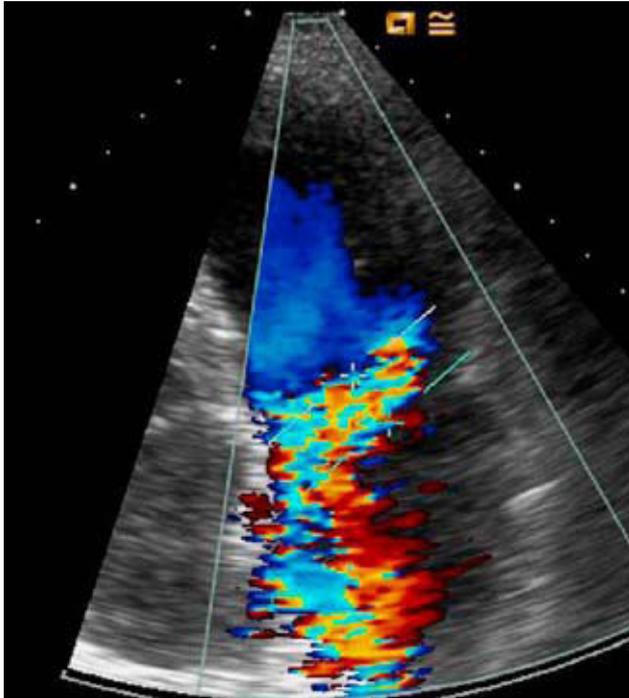

Figure 1   Echocardiographic view, apical plane, four chambers. Acute mitral valve insufficiency is observed, secondary to spontaneous tendinous cord rupture as a complication of pneumonia. One-cm contracted vein. The absence of endocarditis was confirmed at mitral valve prosthesis surgery. Coronariography showed the epicardial coronary arteries to be normal.
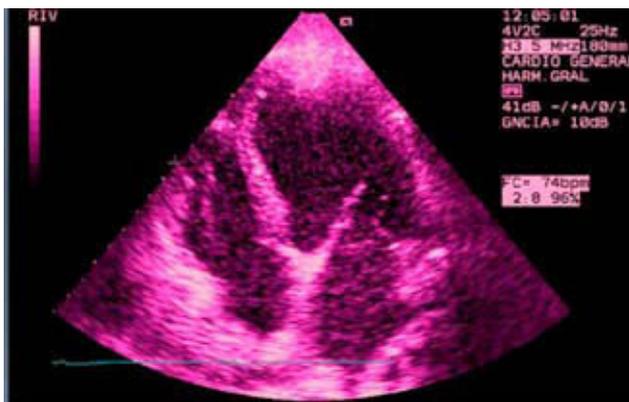

Figure 2   Echocardiographic view of a patient subjected to major abdominal surgery in a state of septic shock due to peritonitis. The left ventricle shows pathological remodeling similar to that seen in the case of anterior acute myocardial infarction. The patient survived and the image normalized.
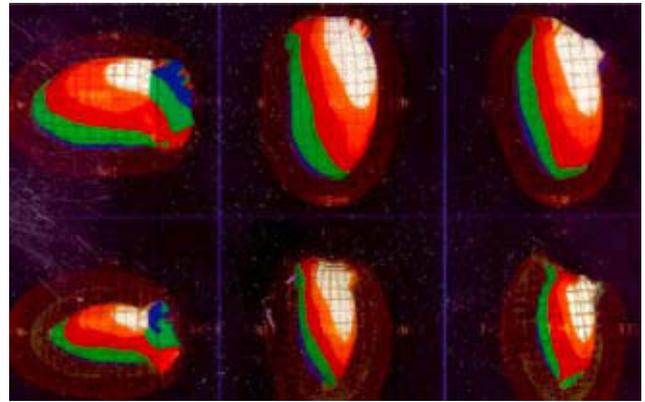

Figure 3   Isotopic image of the previous patient, following recovery from septic shock. The image appears normal, with no evidence of myocardial ischemia. Coronariography showed the epicardial coronary arteries to be normal.

the underlying mechanisms are beginning to become known, and include: 1) myocardial ischemia, 2) systemic inflammatory response, 3) atherosclerosis, 4) the deleterious effects of catecholamines, or even genetic predisposition, etc. However, no ways to attenuate this type of complication have been established, though the advisability of providing cardioprotective therapy for critically ill patients is increasingly recognized. In this context, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) and statins may play an important role. The possible effect of statins in non-cardiovascular pathology is currently the subject of debate. The present study offers a review of the possible effect of statins in critical non-cardiac disease.

The postoperative period of cardiac surgery is characterized by quite significant morbidity-mortality, and cardioprotective measures in the form of statin administration could be advised in such situations. In a retrospective study of 1663 patients subjected to elective aortocoronary bypass surgery, Pan et al.[2] recorded a significant reduction in mortality 30 days after surgery (3.75% versus 1.8%, p=0.01) among the subjects who received statins (943 patients). However, there were no modifications in the incidence of peroperative acute myocardial infarction (AMI), arrhythmias, stroke or renal failure. In contrast, Ali et al.,[3] in a series of 5469 patients subjected to coronary revascularization surgery, observed no benefit derived from the administration of statins. Collard et al.,[4] in a prospective longitudinal study including 5436 patients subjected to elective coronary revascularization surgery, reported significant improvement in overall mortality (in the first 3 days, 1.4% versus 0.3%, p<0.001), though there were no differences in hospital mortality. However, the multivariate analysis showed statin suspension to be independently associated to an increased risk of postoperative cardiac mortality. This possible positive effect of statin treatment could be attributable to antiinflammatory activity. This hypothesis is based on the observation that the administration of simvastatin in patients subjected to coronary revascularization and who require cardiopulmonary bypass gives rise to a reduction in

IL-6 and IL-8 levels, with an increased neutrophil apoptosis rate. This study involved assignment to 40 mg of simvastatin for three weeks before surgery, or to placebo.[5] Chello et al., in a recent metaanalysis of 30,000 heart surgery patients, reported significant benefits derived from the preoperative administration of statins. Such benefits were referred to any mortality of any cause, atrial fibrillation and stroke, though no benefits were noted in terms of peroperative AMI or renal failure.[6] The mentioned study recorded an absolute reduction in mortality in the early postoperative period of 1.5%. Overall mortality in the control group was 3.7%. In addition, clinical observational data could suggest that statin administration is correlated to a significant reduction in heart failure, malignant arrhythmias or cardiac death. The mentioned reduction in cardiovascular events in turn could prove dose-dependent (OR 0.56; 95%CI: 0.32-0.96).[7]

One of the origins of death among patients subjected to major non-cardiac surgery is cardiological mortality – the incidence of which is not clear, though it is believed to be high.[8] Mangano et al., in a cohort of 6237 patients subjected to non-cardiac vascular surgery, reported an incidence of peroperative cardiovascular death or AMI of 2.5% (range 2.0-3.7%), while the corresponding incidence of such complications among patients with pre-existing vascular disease reached 6.6% (2.2-19.0%).[9] Poldermans et al., in a case-control study involving 2816 postoperative patients (overall postoperative mortality 5.6%), found patients treated with statins before surgery to have a lesser postoperative mortality rate (adjusted OR 0.22; 95%CI: 0.10-0.47), despite the fact that these statin-treated patients could have comparatively greater morbidity (receiving such medication as primary or secondary prevention therapy).[10] Over 30 days of follow-up, Kertair et al. recorded a decrease in mortality or peroperative AMI (maintained in the multivariate analysis and in the propensity analysis) in 570 patients subjected to abdominal aortic surgery, associated with the administration of beta-blockers and statins.[11] The most important observational study, at least in terms of the number of patients included and considering the fact that a propensity or trends analyzing model was used, is that published by Lindenauer. This study was carried out in 329 hospitals in the United States, involving 780,591 patients subjected to major non-cardiac surgery. In relation to statin treatment, the patients were included if these drugs were started in the 48 hours prior to surgery. A total of 2185 patients received statins before surgery - these subjects being older individuals, with a greater presence of diabetes, more heart failure or a greater prevalence of hyperlipidemia. Despite these conditions, the gross mortality was lower in the group treated with statins: 3.05% versus 2.13% (p<0.001). These differences persisted upon conducting the multivariate analysis and the trends analysis. The number of patients needed to treat (NNT) with statins in the preoperative period of major surgery was 85 (95%CI: 77-98).[12] The StaRRS study, including 1163 patients, reported a decrease in mortality (adjusted OR 0.52; 95%CI: 0.31–0.99, p=0.046).[13] At present, the Podermans group has detected a high prevalence (11%) of myocardial damage in patients with aortic aneurysms treated via the endovascular route (defined on the basis of troponin elevation).[14] In a

cohort of 220 patients, the gross mortality after 2.9 years of follow-up was 51% in the case of the patients without myocardial damage and 85% in those with cardiac damage (adjusted OR 2.3; 95%CI: 1.1-5.1). However, the group treated with statins showed a reduction in mortality (OR 0.5; 95%CI: (0.3-0.9). The same group developed a mortality predicting score in patients with aortic syndromes, showing that the prior administration of beta-blockers, aspirin and statins exerts a protective effect against mortality.[15] In the same way that statins offer benefit in relation to percutaneous coronary interventions and stent placement, they could reduce restenosis following the procedure (angioplasty or stent) in application to the renal artery or carotid artery.[16]

The PREVENT III observational study showed that patients with critical ischemia of the extremities pre-treated with statins derive clear benefit in terms of mortality after one year. In this study, no such benefit was observed with beta-blockers or aspirin.[17] In addition to the observational studies, the literature offers a limited number of clinical trials. Durazzo et al., in a prospective, randomized and controlled trial, evaluated the efficacy of a single 20 mg dose of atorvastatin during 45 days, versus placebo. The study was carried out independently of the cholesterol levels. Surgery was performed an average of 31 days after randomization. The primary endpoint was the incidence of cardiovascular events, regarded as death of cardiovascular origin, AMI, unstable angina (UA) or stroke. Fifty patients were included in each group. The incidence of the primary endpoint was 26% in the placebo group and 8% in the group treated with atorvastatin (p=0.031). The difference persisted after 6 months (p=0.018). Obviously, in this clinical trial the small sample size must be taken into account.[18]

In contrast to the above, the recent DECREASE IV trial detected no benefit with the administration of fluvastatin. This randomized and controlled factorial trial compared 2.5 mg of bisoprolol versus placebo, and 80 mg of fluvastatin versus placebo. The primary endpoint was the reduction of mortality or peroperative AMI. The study observed benefit with bisoprolol, but not with fluvastatin.[19]

The possible protective action of the statins has also been explored in neurology. Animal studies have identified a probable benefit derived from simvastatin administration in relation to traumatic brain damage.[20] This drug could reduce cell apoptosis and improve sensory function following head injuries. Such benefit could be mediated by activation of the AKt pathway.[21] Based on the inhibition of isoprenoids, experimental models have postulated that pre-treatment with atorvastatin could prevent endothelial dysfunction, facilitate neuroprotection and promote possible recovery after spinal injury.[22] Likewise, experimental animal models could suggest an attenuation of cerebral vasospasm in the context of subarachnoid hemorrhage, after 14 days of prior treatment with simvastatin. Two posterior studies, published in 2006 and 2009, have obtained contradictory results. The first study[23] involved a cohort of 115 patients with subarachnoid hemorrhage, of which 49 developed vasospasms. Of these subjects, 15 (13%) had previously been receiving statins. Prior treatment with statins behaved as a protective variable against subarachnoid bleeding (OR 0.09; 95%CI:

(0.01-0.77). However, in the second study, of an observational nature and involving 170 patients with statins and 170 patients without statins, no such benefit could be confirmed.[24] Another similar study[25] involving 25 patients with subarachnoid hemorrhage treated with statins and 40 patients with subarachnoid hemorrhage not treated with statins recorded benefit after 14 days – the latter being defined as a reduction in brain ischemia, improved functional condition, and improved transcranial Doppler findings. In a controlled phase II trial involving 80 patients with subarachnoid hemorrhage randomized to either 40 mg/day of pravastatin or placebo for 14 days, statin therapy was seen to be safe and effective. In this study, patients who had previously received statins were excluded. At the end of the study, the patients administered pravastatin showed a lesser incidence of cerebral vasospasm and mortality.

Other similar trials, after confirming subarachnoid hemorrhage by angiography, randomized patients to either simvastatin 80 mg/24 hours or placebo. After 14 days, the incidence of vasospasm was lower in the simvastatin group.[26,27]

However, not all authors have found clear benefit with the administration of statins in relation to subarachnoid hemorrhage. One study including 1004 patients with subarachnoid hemorrhage revealed no benefit secondary to the indiscriminate administration of statins. However, the subgroup of individuals previously treated with these drugs, and in whom the medication had been suspended, did show a clear increase in the incidence of subarachnoid hemorrhage.[28] On the other hand, "surprisingly" it has also been suggested in a retrospective study of 514 patients that statin therapy might actually give rise to an increased incidence of subarachnoid hemorrhage.[29]

In patients with ischemic disease, the beneficial effect in relation to a decrease in stroke is clear[30] - such benefit having been firmly established, independently of coronary involvement. Treatment with 80 mg of atorvastatin has been shown to reduce the incidence of stroke. The authors of the randomized SPARCL trial found that on prolonging treatment for 1-6 months after an initial event, stroke recurrence decreases (though the incidence of intracranial bleeding increases), and the number of new cardiovascular events decreases considerably (RR 0.80; 95%CI: 0.69-0.92; p=0.002).[31] In addition to reducing the incidence of stroke, the mortality rate associated to the latter could also decrease. A controlled study found that the cohort pre-treated prior to stroke showed lesser mortality after one month (OR 0.57; 95%CI: 0.35-0.93).[32] The decrease in the incidence of stroke could be similar in the different stroke groups,[33] though lesser benefit may be derived in the case of small-vessel cerebrovascular disease,[34] Nevertheless, it seems that statin administration could increase the incidence of intracranial bleeding in stroke patients receiving thrombolytic treatment (local or systemic) – though this increase in intracranial bleeding does not modify overall stroke mortality,[35] and may even improve it.[36] Based on a metaanalysis of 8832 stroke patients, a decrease in the risk of stroke was recorded. This benefit should not be underestimated, despite the observation of a slight increase in intracranial bleeding.[37] Although the statins may increase the bleeding risk after stroke, they could exert a protective effect against intracranial bleeding. A cohort study involving patients with intracranial bleeding in the John Hopkins Hospital found the early administration of statins to decrease mortality and peri-hematoma edema formation.[38,39] The Israeli NASIS group obtained similar results in a cohort of 3212 stroke patients, of which 312 evolved towards intracranial bleeding. At the time of intracranial bleeding, 89 of the patients were receiving statins. These statin-treated individuals presented less severe stroke, with better outcomes, lesser mortality, and improved cooperation with the nursing personnel, at discharge.[40] Similar data have been published by other authors,[41] proposing that statin administration could alter the survival predicting scores in intracranial bleeding.[42] While though to be similar to the mechanisms implicated in acute coronary syndrome (ACS), the ways in which the statins afford neuroprotection are not well known. On one hand, a reduction in intracerebral cholesterol has been postulated - such reduction occurring in the cerebellum, but not in the brain cortex. What is known is that the statins reduce amyloid production and accumulation – a phenomenon implicated in the intensification of dopaminergic dysfunction underlying Parkinson's disease. Other possible statin activities are: 1) isoprenoids excitotoxicity inhibition, 2) nicotinamide-adenine dinucleotide phosphate instability, 3) stem cell recruitment, 4) reduction of oxidative damage, 5) improvement of vascular function, 6) coagulation inhibition, 7) the promotion of angiogenesis, and 8) modulation of the immune response.[43]

A retrospective cohort study has been made involving 185 patients with chronic obstructive pulmonary disease (COPD) followed-up on for one year. The patients treated with statins suffered fewer acute episodes and required less intubation than the patients not previously administered statins – this situation being explained in terms of an antiinflammatory mechanism.[44] Concomitant COPD and cardiovascular disease is not uncommon, and both conditions are characterized by an inflammatory mechanism. The ARCE study reported a higher prevalence of cardiovascular events among individuals with COPD, and 27% of these individuals were seen to have hyperlipidemia.[45]

In addition, the statins could reduce mortality among patients with COPD overinfected with the human influenza virus.[46] The Poldermans group has evaluated the use of statins in patients with COPD and vascular pathology. Based on an observational study including 3371 patients with vascular disease (of which 1310 also presented COPD), the authors evaluated the administration of low and high statin doses. The primary endpoint was defined as mortality 30 days after vascular surgery. Among the 330 patients receiving statins (25%), lesser mortality was only recorded for those who received high-dose statin therapy.[47] In addition, the statins could contribute to reduce the incidence of mechanical ventilation through modulation of the inflammatory response. This hypothesis is based on the observation that pravastatin might attenuate the inflammatory response in patients with chronic bronchitis,[48] or that simvastatin may attenuate emphysema in smokers and limit the inflammatory response of COPD.[49,50] However, it also would be reasonable to assume that such benefit could derive from the improvement in heart failure usually

associated to patients with COPD, or even that such patients actually may have heart failure instead of COPD. However, the statins have not shown beneficial effects upon mortality among patients with acute lung damage or acute respiratory distress syndrome (ARDS), in the context of a study of 1029 patients,[51] or upon their physiological parameters.[52]

Although no studies have been made of statin action upon mortality in pulmonary thromboembolism, the administration of rosuvastatin could have a preventive effect.[53]

Another potential effect of the statins, and particularly of simvastatin, could be a reduction in portal hypertension, in patients with liver cirrhosis. Abraldes et al., in a randomized, controlled study comparing simvastatin versus placebo, found that treatment with 20 mg/day of simvastatin for one month, with dose escalation to 40 mg/day over the subsequent 15 days, improved portal hypertension and perfusion.[54] The statin might even limit the effect of endotoxemia in the context of liver damage, preventing liver dysfunction.[55] Although not all studies evaluating statin action in relation to transplants have obtained favorable results, many authors have identified reductions in cholesterol, arterial hypertension, in the development of diabetes, the risk of renal failure, vascular disease, transplant rejection rate, and even mortality. Indeed, the therapeutic potentials have also been examined in pediatric transplantation procedures.[56] Renal failure is a potent precursor of atherosclerosis. The Cochran Library has found statins to be safe and effective in renal failure.[57] However, the AURORA trial, involving 2776 patients, found no benefits in terms of a reduction in cardiovascular events, on administering rosuvastatin versus placebo in subjects with renal failure.[58] Likewise, statins were not seen to offer benefit in terms of survival among patients with renal failure enrolled in dialysis programs – though a clear reduction in cholesterol, and a possible decrease in the frequency of sepsis and associated hospital admissions, were recorded.

Obviously, these findings raise questions and generate interest in examining the possible beneficial effects of statin therapy in different situations in critical patients. However, perhaps the greatest interest refers to systemic inflammatory response syndrome, sepsis and multiorgan failure. Simvastatin, and to a lesser extent fluvastatin, have been evaluated against methicillin-sensitive or -resistant *Staphylococcus aureus*, and against vancomycin-sensitive or –resistant enterococcal strains. Propanolol was used as control. Both simvastatin and fluvastatin showed clear antimicrobial effects – the data being particularly significant in the case of simvastatin.[59] Fluvastatin could exert a beneficial effect against *Mycobacterium tuberculosis*. The statins have also shown antifungal properties, particularly against different species of *Zygomycosis* and different species of *Candida*, as a result of reductions in ergosterol. Likewise, a synergic effect has been demonstrated between lovastatin and fluconazole, and between fluvastatin and fluconazole, amphotericin, voriconazole and itraconazole. Moreover, lovastatin and simvastatin could exert fungicidal activity against different species of *Aspergillus*, and against *Cryptococcus neoformans*. In turn, the statins could offer benefit against different viral infections. In this context,

they could reduce the replication of cytomegalovirus, Epstein-Barr virus, hepatitis C virus or human immunodeficiency virus. At present we are facing an H1N1 influenza virus pandemic. In 2006, Felson raised the possibility of deriving benefit from statin treatment against the influenza virus, in the face of an immediate pandemic.[60] At present, and based on a murine model, it has been postulated that the association of statins and caffeine could offer effectiveness similar to that of oseltamivir or ribavirin against the H5N1, H3N2 and H1N1 viruses.[61] Experimental studies of meningococcal meningitis have been used to suggest the possibility that simvastatin might attenuate the inflammatory response in meningitis.[62] Experimental studies in animals suggest that statins could exert an antimicrobial and protective effect against sepsis. Moreover, studies based on human models and fundamentally of an observational nature appear to support this hypothesis. The largest study on the usefulness of statin therapy in septic patients involved a cohort of subjects over 65 years of age admitted due to acute coronary syndrome or stroke, or who required revascularization, and were still alive three months after discharge. The mentioned cohort was based on a Canadian registry in which matched trend analyses were made of 69,168 patients (34,584 patients per group). The incidence of sepsis was lower among the statin-treated patients (71.2 versus 88.0 events per 10,000 patients-year, risk reduction 19%) (RR 0.81; 95%CI: 0.72-0.91). This protective effect against sepsis persisted in the high risk subgroups such as diabetes, chronic renal failure or a history of infections. In addition, there was a significant reduction in severe sepsis (RR 0.83; 95%CI: 0.70-0.97) and fatal sepsis (RR 0.75; 95%CI: 0.61-0.93). In contrast, no benefit was observed with the use of non-statin lipid-lowering agents.[63] Similar results were obtained in other observational studies.[64,65] Based on a series of 22 studies involving 177,260 patients (51,193 and 126,067 with and without statin treatment, respectively), an analysis was made of statin action upon sepsis. A total of 19 cohort studies were examined (7 prospective and 12 retrospective trials), together with two case-control series and one randomized, controlled trial. The efficacy of statin therapy was evaluated in 9 studies including patients with any type of sepsis, four studies involving community-based pneumonia, three studies of bacteremic patients, and three trials involving postoperative patients. The mortality data corresponded to 15 studies comprising a period of 10 years. Mortality was seen to be lower among the patients treated with statins (3 out of 6 sepsis studies, 5 out of 6 community-based pneumonia trials, and 2 out of 3 studies of bacteremia). Four studies showed no differences in mortality, while one study reported increased mortality among the patients administered statins. Five of the 9 studies, in which the primary endpoint was the risk of sepsis or infection in relation to statin use, a reduction in risk was recorded among the subjects receiving statins, while the rest of the studies reported no differences. Most of the patients receiving statins in the different studies showed a higher prevalence of cardiovascular disease, greater comorbidity, and more diabetes, hypertension, hyperlipidemia and renal failure, older age and even higher APACHE II scores. Despite this

fact, however, most of the studies globally and independently of the design involved (adequate matching, randomization, etc.), suggested that statins exert a beneficial effect in terms of infection, with lesser mortality, shorter hospital stay and fewer complications (particularly in those studies conducting trend analyses). However, most of the mentioned studies were of an observational nature, and no firm conclusions could be drawn.[66] The effect of statin therapy has been evaluated in a cohort of 188 septic patients over 40 years of age, admitted to Intensive Care in the period 2005-2006. Of these subjects, 60 (32%) had previously been receiving statins. Both groups were homogeneous in terms of age, sex and APACHE II score. Gross mortality was lower among the statin-treated patients, with a relative mortality reduction of 35% (31.7% versus 48.4%; p=0.040). The greatest reduction in mortality, attributable to statin administration, corresponded to the subgroup of more seriously ill patients, with APACHE II scores of over 24 points (32.3% versus 57.5%, p=0.031) – no differences being recorded in the less severe subgroup (APACHE II scores ≤ 24 points; 31.0% versus 36.4%, p=0.810). The multivariate analysis attributed benefit to the administration of statins in relation to mortality (OR 0.42; 95%CI: 0.21-0.84; p=0.014).[67] *A priori*, this could have been simply another observational study evaluating the effect of statins upon severe sepsis. However, it postulated an interesting hypothesis whereby statin benefit might be seen in the subgroup of more seriously ill patients. The statins moreover could offer special benefit in the more seriously ill subgroups in terms of the prevention of pneumonias or even the reduction of mortality due to such pneumonic processes. A case-control study of 4719 diabetic patients who developed pneumonia and 15,322 controls showed active statin therapy to significantly reduce the incidence of pneumonic processes (adjusted OR 0.49; 95%CI: 0.35-0.69). However, previous statin use, regarded as administration one year before the development of pneumonia, and current non-utilization of statin drugs, were not associated to a reduction in pneumonia risk (OR 0.95; 95%CI: 0.663-1.42).[68] Chalmers et al.[69] conducted a prospective observational study of patients admitted due to community-acquired pneumonia in the period 2005-2007. The authors evaluated mortality after 30 days, the need for mechanical ventilation, or the need for inotropic support. Despite the fact that the statin-treated group presented more serious initial pneumonia, those subjects who received statins had lower C-reactive protein values (119 mg/l versus 182 mg/l; p<0.0001). In addition, the adjusted OR for mortality among the statin-treated patients was 0.46 (95%CI: 0.25-0.85; p=0.006). However, there were no significant differences between the need for mechanical ventilation or inotropic support. These benefits in terms of diminished mortality have also been reported in other cohort studies.[70]

A randomized, double-blind clinical trial evaluated the incidence of severe sepsis and inflammatory response with statin treatment. A total of 83 patients with established bacterial infection were randomized to either simvastatin or placebo. Due to low recruitment, the study was prematurely suspended, and no differences in the incidence

of severe sepsis were recorded – though simvastatin treatment was seen to lead to a decrease in TNF and IL-6 concentrations.[71]

In addition to the possible beneficial effects in relation to sepsis, the statins might also exert a protective effect against other models of systemic inflammatory response, such as post-resuscitation syndrome,[72] hemorrhagic shock[73] or acute pancreatitis,[74] and may even improve mortality among patients with multiorgan failure.[75] Leukocyte recognition of microbial products and other immune cells represents the basis of innate immune response and sepsis. Toll-like receptors (TLRs) facilitate immune system adaptation, and are responsible for the recognition of certain pathogens and for stimulation of the host immune response to such pathogens. Once the TLRs have been activated, they trigger an intracytoplasmic molecular response and initiate the inflammatory reaction and the expression of adhesion molecules at vascular endothelial level. This response can be interfered with by lovastatin, which inhibits the CD11b surface receptors – thus hindering monocyte adhesion to the endothelium. Bacterial components in turn react with the TLRs, and are believed to act as trigger factors for monocytes, neutrophils and endothelial cells – resulting in initiation of the inflammatory cascade. This process in turn gives rise to an increased production of proinflammatory molecules such as TNF, IL-1, IL-6, IL-8, lysosomal enzymes, superoxide radicals and vasoactive substances such as platelet activating factor, tissue factor and plasminogen activator inhibitor-1 (PAI-1). The above mechanism develops in combination with an increase in the endothelial expression of nitric oxide (NO). In situations of stress or endothelial dysfunction, endothelial nitric oxide synthase (eNOS) production decreases, though simultaneous over-expression of inducible nitric oxide synthase (iNOS) (practically inactive under normal conditions) is observed. This gives rise to NO over-production, with bactericidal activity, but also generates important vasodilatation and activation of the inflammatory pathway. In sum, an imbalance is observed between eNOS and iNOS, leading to coagulopathy, endothelial dysfunction, vascular instability, eventual cell apoptosis and multiorgan failure.[76] In this line, new molecules known as nitrostatins are being developed, such as nitropravastatin or nitroatorvastatin.[77] The mentioned endothelial damage, which is particularly important at pulmonary level, is generalized and probably plays a key role as the cause of dysfunction and multiorgan failure. In addition, in sepsis, endothelial dysfunction giving rise to a proinflammatory, prothrombotic and proapoptotic state is observed. *In vivo* studies have shown that simvastatin and lovastatin prolong the half-life of iNOS. In addition, the statins inhibit endothelial NO expression, with possible improvement in hemodynamic response – reducing TNF, interferon, NF-kB transcription via its induction signal and the activation of transcription. The statins exert antiapoptotic activity through the modulation of eNOS. In situations of sepsis, circulating nuclear protein matrix levels increase in correlation to cell death, and even cell apoptosis is observed, in relation to endothelial NO. The imbalance between eNOS and iNOS can modify mRNA levels and thus protein expression.

Likewise, the excessive vasodilatation caused by the generation of NO could be countered by the statins. It has been postulated that the coadministration of simvastatin may reinforce the effects of phenylephrine in experimental models and help maintain muscle tone. The inflammatory process generates systemic tissue damage, particularly at endothelial level. Proinflammatory cytokines are released, with an increase in the expression of adhesion molecules and transmigration towards the postcapillary venules. The process includes activation of the selectin protein family, specifically selectins E (endothelium), P (platelets), and L (leukocytes). Adhesion implies integrins 2, CD 11b and CD18, LFA 1, which are expressed by the leukocytes and bind ICAM-1, ICAM-2 and ICAM-3 in the vascular endothelium – these molecules being responsible for the trans-endothelial migration of the leukocytes. The Rho proteins, which act as molecular switches in a range of cell signaling pathways, or in cell cytoskeletal modulation, activate the nuclear factor-B. The statins could inhibit the Rho proteins through intermediate mevalonate inhibition pathways. In addition, the inflammatory process could be limited through activation of the function of type I T helper lymphocytes.[78] The administration of statins moreover could limit the production of different cytokines such as IL-6, IL-8 and TNF, as well as the chemotactic effect of monocytes and C-reactive protein. The latter is produced fundamentally in the liver, and essentially in response to IL-6. Simvastatin and atorvastatin inhibit IL-6 and therefore C-reactive protein. The statins could reduce molecular adhesion not only mediated by leukocyte action but also through activation of the signaling cascade for leukocyte transmigration. In addition, the statins could block the effects of the cytokines and intestinal bacterial translocation.[79]

Despite the extensive literature on the benefits of the administration of statins in infectious processes, most of the studies are of an observational nature, with potential sources of bias[80,81] – particularly "well treated" patient selection bias. An example of this is represented by patients with sepsis and heart failure treated with statins and also beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) (i.e., well treated subjects), while the same patients treated without statins could likewise have been treated without beta-blockers or without ACEIs. Theoretically, such bias could be resolved through trends analysis, though not all studies use such analysis or adequate matching of cases. In any case, these are largely observational studies, and the possibility of bias therefore cannot be excluded. Another potential source of bias is the desire to publish – particularly in the case of studies reporting positive results – or even a possible lucrative factor.[82] In the field of Cardiology there are many randomized and controlled studies reporting evidence of benefit in the administration of statins with respect to cardiac protection.[83] The methodologies and populations of such studies are more solid and potent than those in other fields of Intensive Care Medicine – a fact that makes comparisons difficult. However, although such evidence is lacking in the rest of the areas of non-cardiac Intensive Care Medicine, it has been suggested that the administration of statins could also exert a protective effect, and we probably should reconsider the suspension of statin administration in those patients in our ICUs who have previously received such medication.[84] In addition to the critical care setting, statins have also yielded promising results in relation to control of the incidence and progression of other disease conditions such as Alzheimer, multiple sclerosis, dementia, autoimmune diseases (particularly rheumatoid arthritis), gastrointestinal disorders (including probably also a decrease in colon cancer), bone disease, osteoporosis or even macular degeneration.[85] Such benefits remain to be confirmed, however.

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