The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are the most commonly prescribed agents for hypercholesterolemia and have revolutionized the management of hyperlipidemia and the area of cardiovascular risk reduction. However, recent data suggest that their effects go well beyond the lipid lowering seen with long-term use and may include acute antiinflammatory activity, anticoagulation, immunomodulation, as well as promotion of changes in smooth-muscle tone. Because of these data, promising research has begun into the use of these agents in various critical care areas such as the early phases of sepsis, bacteremia, and ischemic stroke. Recent data also show a decrease in cerebral vasospasm after subarachnoid hemorrhage, an area deficient in therapeutic options. More research is necessary to ascertain the true role of statins in the treatment of these various disorders. Nevertheless, the concept of a statin's role as being only a routine preventive therapy with benefits limited to patients undergoing extended treatment is rapidly becoming inaccurate.

Key Words: statins, critical care, 3-hydroxy-3-methylglutaryl reductase inhibitors, HMG-CoA reductase inhibitors, sepsis, bacteremia, subarachnoid hemorrhage, stroke, pleiotropy.

(Pharmacotherapy 2007;27(9):1279–1296)
Pleiotropic Effects

The pleiotropic activities of statins are numerous and wide ranging. Evidence of antiinflammatory, immunomodulatory, and anticoagulant effects have been demonstrated with several different statins. Although the full extent of this activity is still being explored, the available basic science data provide the groundwork for encouraging clinical research in this area.

Antiinflammatory Effects

The antiinflammatory effects of statins are integrated into a multitude of pathways. Modulation of nitric oxide production by statin therapy may optimize nitric oxide availability in acute inflammatory states. Vascular proliferative changes due to inflammation are suppressed by statins, as are immunostimulatory adhesion molecules. Clinical biomarkers of inflammation such as C-reactive protein are also decreased by statins, providing further evidence of their general antiinflammatory activity.

Nitric oxide is a potent, local vasodilatory substance produced by the vascular endothelium and is necessary for optimal vessel patency and perfusion for a variety of human tissues. Endothelial cells are thought to secrete nitric oxide when exposed to sheer stress. Statin use was found to be a significant predictor of arterial dilation, and this effect was found to be positively correlated with the dose, with those in the high-dose group (simvastatin 20 mg, lovastatin 40 mg, pravastatin 40 mg) having the greatest dilation (p<0.05 for trend). Statins appear to increase the amount of endothelium-derived nitric oxide synthase (eNOS) within the vascular endothelium, subsequently increasing the availability of nitric oxide.

Increasing the amount of eNOS confers antiinflammatory effects through inhibition of leukocyte and platelet adhesion. In addition to increasing eNOS concentrations, statins may have a decremental effect on the inducible form of nitric oxide synthase (iNOS). Excessive activation of iNOS is a common manifestation of inflammation that has been implicated in neuronal cell death during ischemia and the profound vasodilation often seen in distributive shock. The effects of statins on nitric oxide appear to be relatively rapid in onset. Acute increases in nitric oxide production and improvement of endothelium-dependent vasodilation have been shown to be some of the earliest measurable effects of therapy and occur far before any lipid effects. In animal models, simvastatin therapy 50 or 100 µg/kg was shown to increase eNOS expression and decrease endothelial cell P-selectin expression by 50% within 18 hours of administration. These regulatory actions on eNOS and iNOS result in statins serving a potentially protective role in the setting of acute inflammation by preserving the balance of nitric oxide availability in the vasculature.

Statins also appear to affect inflammation through antagonism of smooth-muscle cell proliferation and immune cell recruitment. The adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), are commonly associated with tissue damage and inflammation in the setting of myocardial infarction and stroke. The VCAM1 and ICAM1 are downregulated by statins, thereby blunting the immune-mediated inflammatory response. In smooth-muscle cells, statins have demonstrated antiproliferative and proapoptotic effects, further supporting a role for these drugs after injury. The proposed mechanisms for these effects include the induction of cell-cycle arrest, increases in proapoptotic gene expression, and a reduction in the synthesis of isoprenoids. Current data suggest that the impact of statins in this setting is largely independent of its lipid-lowering ability, as other nonstatin hypercholesterolemia agents have not been shown to have this effect.

Immunomodulatory Effects

The influence of statins on immune function seems to be multifactorial. They have demonstrated effects not only on chemokine production, but also on reducing T-cell activation. These actions may be mediated through inhibition of major histocompatibility class II antigen expression. This is reflected in early data showing macrophage growth suppression by statin therapy. Statins also appear to affect tissue factor, as demonstrated in 20 healthy men randomly assigned to receive either simvastatin 80 mg/day or placebo daily for 4 days before intravenous administration of lipopolysaccharide 20 IU/kg in a double-blind, placebo-controlled, parallel-group study. Statin premedication inhibited increases of monocyte tissue factor expression after 4 and 8 hours. It also reduced endotoxin-induced formation of prothrombin fragment 1 + 2 over the same time period, demonstrating a suppressive effect on the
inflammatory response to endotoxin. Statins also appear to alter the cytotoxicity of natural killer cells, as evidenced by their effects on the inhibition of acute renal xenograft rejection.\(^2^8\)

A separate hypothesis proposes that the increase in LDL receptors may be beneficial in the setting of lipopolysaccharide exposure by internalizing the toll-like receptor-4 and subsequently inhibiting the ubiquitous proinflammatory transcription regulator, nuclear factor–κ B.\(^2^9\) Further research has also demonstrated that statins interfere with exotoxin-induced leukocyte-endothelial cell interactions, leading researchers to ponder the adjuvant role of these agents in the treatment of infection.\(^1^7\)

**Anticoagulant Effects**

The tight interrelation of the immune system, inflammatory response, and coagulation pathways makes it no surprise that statins also exhibit antiplatelet and anticoagulant properties. Statins appear to affect coagulation by decreasing platelet aggregation and adhesion through eNOS activity and direct inhibition of platelets.\(^3^0, 3^1\) Through their ability to inhibit platelet expression of the protease-activated receptor-1 (PAR-1) thrombin receptor, statins decrease the attraction of thrombin to the platelet's surface.\(^3^2, 3^3\) Significant inhibition of PAR-1 platelet expression has been observed in patients taking various statins after only 4 weeks of therapy.\(^3^4, 3^5\) As thrombin is essential to the conversion of plasma fibrinogen and ensuing clot formation, statins have potential to exert a profound effect on thrombosis and platelet aggregation.\(^3^6\)

Statins also appear to increase the activity of thrombomodulin and tissue plasminogen activator, leading to an anticoagulant effect.\(^3^6, 3^7\) Specifically, atorvastatin and simvastatin have been shown to increase transmembrane glycoprotein thrombomodulin expression. In practice, this may increase thrombomodulin-thrombin complexation, which leads to a decrease in thrombin's procoagulant potential and an increase in activation of the antiinflammatory-anticoagulant protein C. The end result is the inherent activity of statins to inhibit coagulation and promote fibrinolysis in the setting of inflammation, endothelial dysfunction, and protein C deficiency.\(^3^7\) These insidious anticoagulant effects may be an important contributor to the short-term effects of statins in the setting of a procoagulant state such as acute coronary syndromes, ischemic stroke, and sepsis.

**Discontinuation Effects**

Further support for the short-term effects of statins is evidenced by the discontinuation of statin therapy, which also seems to produce rapid results. Abrupt discontinuation has been shown to lead to a rebound effect and the precipitation of adverse consequences. For example, statin withdrawal results in suppression of eNOS production and leads to levels that are below baseline, an effect demonstrated in animal models.\(^3^8, 3^9\) The beneficial effects on platelet function and neuronal cell protection also appear to be nullified after withdrawal of statin therapy, potentially as soon as 2 days after discontinuation.\(^3^9\) There is also a rise in oxygen free-radical production as well as chemoattractant and tissue factor levels after abrupt discontinuation of therapy.\(^4^0, 4^1\) In theory, the removal of these agents in the setting of acute injury would then amplify the developing effects of inflammation and coagulation, leading to an increased risk of ischemia, stroke, and myocardial infarction. This phenomenon has been illustrated in the clinical setting by worsened outcomes in patients with acute coronary syndromes and subarachnoid hemorrhage in whom statin therapy was not continued during the acute illness.\(^4^2, 4^3\)

**Role of Statins in Acute Diseases**

**Bacteremia**

The demonstration of statins as inhibitors of leukocyte rolling, adherence, and transmigration has resulted in increased research into the potential impact of statin therapy on infectious diseases.\(^1^7\) A MEDLINE-PubMed search (1966–January 2007) was conducted combining the terms “statins” and “bacteremia” for the identification of primary research studies. Articles were excluded if they were conducted in animals or if the articles were not in English. The studies evaluating statins in bacteremia are summarized in Table 1.\(^4^4–4^7\)

One retrospective study assessed the effect of statin therapy on mortality due to bacteremia.\(^4^4\) Data of 438 patients with positive blood cultures were reviewed, and 28-day mortality was assessed. Of these patients, 66 (15%) were receiving statins on admission, of whom 56 (85%) continued therapy. Specific statin use was divided among simvastatin (36 patients), atorvastatin (22), and pravastatin (8). Overall, hospital mortality (odds ratio [OR] 0.4, 95% confidence interval [CI] 0.17–0.9) and deaths
attributable to bacteremia (OR 0.06, 95% CI 0.01–0.44) were lower in the group that received statins before admission compared with those who did not. Even more impressive was that in those patients in whom statin therapy was continued on admission (85%), both the hospital mortality rate (OR 0.058, p=0.0002) and deaths attributable to bacteremia (p=0.0018) were 1.8%,
Weant and Cook

significantly lower than those rates in patients not receiving statins. After using multivariate regression to control for significant baseline differences, statin therapy continuation was equally beneficial (OR 0.058, 95% CI 0.008–0.43, p=0.0055).

Although the primary objective of this retrospective study was to establish a relationship between 28-day hospital mortality and statin use, the most interesting result was the observation that discontinuation of previous statin therapy may result in an increase in mortality risk. Because of the retrospective design of the study, it is not possible to establish this fact with certainty. Another confounding fact is that no data on the duration of previous statin therapy were reported, both patients who were maintained with statin therapy for several years and those who started 1 week before admission would have been included in this group. Further complicating the issue is the lack of information regarding the specific bacteremias, occurrence of sepsis, and overall treatment of these patients. No data were reported regarding appropriate and timely antimicrobial therapy or use of other therapies such as drotrecogin alfa (activated) and intensive insulin therapy that may have affected survival in these patients with bacteremia in an intensive care unit (ICU). This study, however, did provide some of the first evidence that discontinuation of statin therapy may adversely affect the outcome of patients in the ICU.

Another group reviewed the records at a Veterans Affairs medical center of 388 bacteremic episodes that were due to aerobic gram-negative bacilli and Staphylococcus aureus over a 5-year period. Patients who were taking a statin at the time of admission and who continued that therapy throughout the course of hospitalization were included in the statin group. The length of therapy, outpatient compliance, and efficacy of lipid lowering were not assessed. The primary outcome of interest was all-cause in-hospital mortality. Thirty-five patients (9%) were taking a statin before admission, with the most common being simvastatin (14 patients). Baseline characteristics showed that most patients were male (386 patients) with an average age of 63 years. The statin group did have higher rates of diabetes mellitus, hypertension, and coronary artery disease (p<0.001).

The source of infection was noted to vary between groups, with a higher rate of pulmonary infections in those who did not receive a statin versus increased skin and soft tissue infections among those who received statin drugs, likely attributable to the difference in the rate of diabetes between the two groups. Overall,

Table 1. (continued)

<table>
<thead>
<tr>
<th>Study Limitations</th>
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<tr>
<td>Retrospective design; duration of previous statin therapy unclear; no data on antimicrobial therapy; concomitant ICU care unclear</td>
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<tr>
<td>Retrospective design; duration of previous statin therapy unclear; no data on antimicrobial therapy; concomitant ICU care unclear</td>
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<tr>
<td>Multiple baseline variations; long-term statin users only; duration of previous statin use unclear; no statin dosage information</td>
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<tr>
<td>Statin users more likely to be admitted with cardiac diseases; limited data on statin therapy before admission</td>
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<tr>
<td>Lack of data on concomitant ICU care; no statin dosage information; no data on statin continuation on admission</td>
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<tr>
<td>Retrospective design; no dosage information; no predefined pneumonia protocol; significant differences in baseline characteristics</td>
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<tr>
<td>Retrospective design; no data on type, dosage, and duration of previous statin therapy; significant differences in baseline characteristics</td>
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<tr>
<td>Retrospective design; no dosage information</td>
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<tr>
<td>Limited to medical ICU population; no data on continuation of statin therapy on admission</td>
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<tr>
<td>No data on type, dosage, and duration of previous statin therapy; significant baseline differences in comorbidities</td>
</tr>
<tr>
<td>No data on specific statin therapies, dosages, previous duration of therapy, or continuation on admission; underlying comorbidities not reported</td>
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urinary tract infections were the most frequent source of bacteremia in both groups. All-cause in-hospital mortality was lower in patients receiving statins compared with those who were not (OR 7.63, 95% CI 1.01–57.5). The rate of mortality secondary to infection was also lower in the patients receiving statins (3% vs 20%, p=0.01). No significant correlation was found between the organism causing the bacteremia and a benefit of statin therapy. An interesting finding was a significant decrease in mortality attributable to hospital-acquired bacteremia in the statin group (0 vs 40 patients, p=0.004).

This study is limited by its retrospective design; however, it is the most detailed study in its assessment of baseline characteristics, comorbid disease states, concomitant drugs, and infectious causes. The most interesting contribution of this study was the detailed analysis of source and pathogenic bacteremia and the fact that the benefits of statin therapy appear to be independent of infection site and causative pathogen. This study demonstrated similar decreases in mortality due to bacteremia when compared with the previously mentioned study, providing further support for the potential effects of statins in patients with bacteremia. Again in this study, duration of previous statin therapy was not

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**Table 1. Studies Evaluating Statin Effects in Acute Disease Processes (continued)**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome Measure (intervention vs comparator)</th>
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<tr>
<td>Vasospasm (continued)</td>
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<tr>
<td>Prospective, matched, controlled cohort</td>
<td>624 patients with subarachnoid hemorrhage</td>
<td>20 patients treated with statins before admission</td>
<td>40 matched controls</td>
<td>14-day BI score: 77 vs 39, p=0.003</td>
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<td>Lawson-PSMS score: 12 vs 19, p=0.03</td>
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<td>Rate of DCI: 10% vs 43%, p=0.02</td>
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<td>Cerebral infarctions: 25% vs 63%, p=0.01</td>
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<td></td>
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<td></td>
<td>Change in TCD mean velocity of ≥ 50 cm/sec: 18% vs 51%, p=0.03</td>
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<tr>
<td>Phase II, randomized, placebo-controlled</td>
<td>80 patients with subarachnoid hemorrhage</td>
<td>40 patients treated with pravastatin 40 mg/day for 14 days</td>
<td>40 patients received placebo</td>
<td>Occurrence of vasospasm: 17 vs 25 patients, p=0.006</td>
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<td>Severe vasospasm: 7 vs 12 patients, p=0.044</td>
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<td>Vasospasm-related DID: 2 vs 12 patients, p&lt;0.001</td>
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<td>Mortality: 2 vs 8 patients, p=0.037</td>
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<tr>
<td>Randomized, placebo-controlled, pilot</td>
<td>39 patients with subarachnoid hemorrhage</td>
<td>19 patients treated with simvastatin 80 mg/day for 14 days</td>
<td>20 patients received placebo</td>
<td>Cerebral vasospasm: 5 vs 12 patients, p&lt;0.05</td>
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<td>Maximum mean MCA TCD velocity: 103 vs 149 cm/sec, p&lt;0.01</td>
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<tr>
<td>Retrospective chart review</td>
<td>514 patients with subarachnoid hemorrhage</td>
<td>36 patients treated with statins previously</td>
<td>No statin</td>
<td>Occurrence of vasospasm: 17 vs 25 patients, p=0.006</td>
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<td>Severe vasospasm: 7 vs 12 patients, p=0.044</td>
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<td>Mortality: 2 vs 8 patients, p=0.037</td>
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<tr>
<td>Ischemic stroke</td>
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<tr>
<td>Retrospective chart review</td>
<td>143 patients with nonlacunar MCA infarct</td>
<td>38 patients treated with statins previously</td>
<td>No statin</td>
<td>Infarct volume: 15.5 vs 25.4 cm³, p=0.054</td>
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<tr>
<td>Retrospective chart review</td>
<td>615 patients with admission for ischemic stroke</td>
<td>205 patients treated with statins before admission</td>
<td>410 matched controls</td>
<td>1-mo mortality rate: 3.9% vs 7.3%</td>
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<td>2.4-yr follow-up mortality: 13% vs 20%</td>
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<tr>
<td>Substudy analysis from phase III citicoline trial</td>
<td>852 patients with acute ischemic stroke</td>
<td>129 patients received statins before admission</td>
<td>600 patients with no statin</td>
<td>NIHSS score of ≤ 2:</td>
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<td>statins before stroke: p=0.07</td>
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<td>statins after stroke: p=0.002</td>
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<td>MRS score of ≤ 2:</td>
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<td>statins before stroke: p=0.08</td>
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<td>statins after stroke: p=0.033</td>
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</table>

ICU = intensive care unit; OR = odds ratio; CI = confidence interval; HR = hazard ratio; DID = delayed ischemic deficits; BI = Barthel Index; Lawton-PSMS = Lawton Physical Self-Maintenance Scale; DCI = delayed cerebral ischemia; TCD = transcranial Doppler ultrasonography; MCA = middle cerebral artery; NIHSS = National Institutes of Health Stroke Scale; MRS = Modified Rankin Scale.
Weant and Cook assessed, although all therapy was continued during admission. Appropriate and timely antibiotic therapy was also not assessed in this study, which may be a potential confounder.

A prospective study investigated the association between statin use within the previous year and mortality among patients with bacteremia over a 6-year period. A total of 5353 patients (42% women) with a median age of 72 years who were hospitalized with a first episode of bacteremia were reviewed. Of these, 176 (3.3%) were noted to have taken at least one statin before admission (48% simvastatin, 28% pravastatin, 18% atorvastatin, 13% other statins) with no dosages reported. Patients receiving statins were less likely to be older than 80 years or have a history of cancer or pulmonary disease; however, they were more likely to have cerebrovascular disease, diabetes, or a previous myocardial infarction (p values not reported). The 30-day mortality rates between statin users and nonusers were similar (adjusted mortality rate ratio (aMRR) 0.93, 95% CI 0.66–1.30). In contrast, among survivors after 30 days, the previous statin therapy group demonstrated a decreased mortality rate up to 180 days after the initial bacteremic event (aMRR 0.44, 95% CI 0.24–0.80). These mortality trends were consistent among both community-acquired and nosocomial bacteremic episodes. There was an observed decrease in the risk of new episodes of bacteremia diagnosed within 180 days after the first bacteremia in the statin group, with an adjusted 30-day incidence rate ratio of 0.45 (95% CI 0.19–1.09) and a 31–180-day incidence rate ratio of 0.5 (95% CI 0.22–1.13).

This study provides one of the largest prospective collections of data on the impact of statin therapy on bacteremia. The results are limited, however, by the multiple differences in baseline characteristics and comorbidities between the two groups. The level of the Charlson Index score, a measure of comorbidities, was medium to high in 84% of the statin users, compared with only 66% of the nonusers. This may in part explain the discontinuous results of this study and the isolated benefit of statin therapy observed (> 30 days). However, this study may also suggest that the effect of statin therapy is not fully realized until weeks after the initial insult. This population is distinct from that of other studies in that this study assessed patients who were documented long-term users rather than those who had just started therapy. How this may affect the results is unclear, as these patients may or may not be more compliant over time or have better access to health care. Although the documentation of specific statin therapy is a positive aspect, the study is limited by the lack of information regarding statin dosing.

Although most data on statins are encouraging, one retrospective cohort analysis of 438 patients in an ICU who were receiving mechanical ventilation for more than 96 hours provides evidence to the contrary. Statin users were compared with nonusers with regard to ICU-acquired infections and hospital mortality. Thirty-eight patients were classified into the statin group; they had been receiving simvastatin 40 mg before admission and had that therapy continued throughout their hospitalization.
Patients receiving statin therapy were significantly older (71.7 yrs vs 61.5 yrs, p=0.001) and were more likely to have a chronic illness as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II (42% vs 26%, p=0.04) than patients not receiving statins. Statin users were also more likely to be admitted for cardiac diseases (34% vs 10%, p=0.001), whereas nonusers were more likely to be admitted for trauma (0% vs 21%, p=0.01). This study found that the ICU-acquired infection rate in statin-treated patients was nonsignificantly lower (29% vs 38%, p=0.3) and the time to infection was greater (median 12 vs 10 days, p=0.6). Length of stay in the ICU was significantly less in the statin group (11 vs 16 days, p=0.02), although the ICU mortality rate was not significantly different (47% vs 34%, p=0.09). Of interest, overall hospital mortality was significantly higher in statin-treated patients (61% vs 42%, p=0.03), even after adjustment for APACHE II predicted risk (mortality ratio 1.53 vs 1.17, p=0.02).

This study is distinctive in that, as a result of financial constraints at their institution, all patients received a standardized statin and dosage. Nevertheless, the results of this study are difficult to interpret due to variations in baseline comorbidities. The significantly higher number of patients admitted to this medical-surgical ICU with cardiovascular diseases in the statin group is concerning in that these patients may have already progressed too far to benefit from the preventive actions of statin therapy. Although the authors attempted to control for this, it may also represent selection bias as significantly more, presumably healthy patients not receiving statins were admitted secondary to trauma. No information was provided on the duration or type of statin therapy before admission. The concerns raised by this study, however, highlight the necessity for more prospective studies on statins in this early period to establish their true effects.

Sepsis

It has been estimated that sepsis occurs in more than 750,000 individuals in the United States annually. Of these, about half require intensive care and almost one third do not survive. The average length of stay is nearly 20 days and results in a cost of more than $20,000/case. Despite the significance of this disease, research into fully elucidating the cause and mechanisms involved are still ongoing. Currently available information suggests that an initial toxic stimulus, such as bacteremia, initiates a cascade of events involving tumor necrosis factor and interleukin-1 that results in cell adhesion, clotting activation, and an overwhelming perpetuation of the initial inflammatory and coagulation response. These events most often lead to organ failure and an increase in the associated mortality. The abilities of statins to affect inflammation, coagulation and protein C activation, and immune cell function may help to counteract this process. In addition, the positive effects statins may have in the setting of bacteremia, present in greater than 17% of sepsis cases, could extend to benefits in sepsis.

A MEDLINE-PubMed search (1966–January 2007) was conducted combining the terms “statins” and “sepsis,” and “statins” and “pneumonia” for the identification of primary research studies. Articles were excluded if they were conducted in animals or if the articles were not in English. The studies evaluating statins in sepsis are summarized in Table 1.

To analyze a statin’s effect on the development of severe sepsis and the progression of organ dysfunction, a retrospective cohort study evaluated the data of 53 patients admitted with sepsis, 16 of whom were receiving statins before admission and 37 who were not. Sepsis was defined, according to the American College of Chest Physicians and the Society of Critical Care Medicine, as suspected or proven infection with at least two of the four systemic inflammatory response syndrome criteria. Outpatient pharmacy records and admission histories were used to determine whether patients had been taking statins before admission. Most patients were taking pravastatin (75%), followed by atorvastatin (13%), then simvastatin (6%), and lovastatin (6%). Patients in the statin group tended to be older and were more likely to have a history of stroke or diabetes mellitus, whereas those in the control group were more likely to have a history of cirrhosis and high bilirubin levels. The authors found that preadmission statin therapy, compared with no statin therapy, was associated with a 30% absolute reduction in the rate of severe sepsis (56% vs 86%, p<0.02). The rate of cardiovascular dysfunction, defined as hypotension requiring vasopressor therapy, was also significantly lower in the statin group (38% vs 73%, p<0.02). However, in-hospital mortality was not significantly different between the two groups.
Weant and Cook

Potential Roles for Statins in Critically Ill Patients

This study was limited by the lack of the inclusion of confounders that may affect the progression to severe sepsis and mortality in the ICU, including antibiotic usage, early goal-directed therapy, and treatment of adrenal insufficiency. Also, it is unclear how many of the patients already had severe sepsis at presentation, in which case the proposed benefit of statin therapy may be blunted. The use of outpatient records to provide written documentation of previous statin usage was beneficial, as was the reporting of the actual statins used. However, data were lacking with regard to the actual dosages of these drugs and whether or not they were continued on admission, a potentially significant confounder.

To examine the effect of statin therapy on the occurrence of pneumonia in an at-risk population, a retrospective case-control study was conducted of the data from 4719 patients with a diagnosis of diabetes and pneumonia and compared with the data from 15,322 matched controls. Patients were defined as those older than 18 years who had their first medical attendance for an episode of community-acquired pneumonia. Each case was matched based on sex, age, general practice, and index date. Patients were classified as current statin users when the diagnosis date was between the start and end date of prescription records. Statin therapy was actively prescribed in 50 (1.1%) of the 4719 cases and in 318 (2.1%) of the 15,322 controls. After adjusting for potential confounders, treatment with statins in both groups was associated with a significant reduction in the risk of pneumonia (adjusted OR 0.49, 95% CI 0.35–0.69). The adjusted ORs for the different statins were 0.57 (95% CI 0.30–1.11) for atorvastatin (57 patients), 0.48 (95% CI 0.14–1.71) for cerivastatin (17 patients), 0.37 (95% CI 0.10–1.31) for fluvastatin (19 patients), 0.36 (95% CI 0.17–0.75) for pravastatin (47 patients), and 0.52 (95% CI 0.35–0.76) for simvastatin (228 patients). Previous use of statin therapy, defined as a history of use during the year before the index date but not currently taking, was not associated with a decreased risk of pneumonia (OR 0.95, 95% CI 0.663–1.42).

This study was distinctive in that the authors not only documented the various statin therapies that individual patients were receiving, but also provided statistical results on the effects of these different statins. However, this study does omit the necessary dosages of these agents to apply these important results. It is also difficult to analyze these results because no predefined protocol was used for diagnosing community-acquired pneumonia, potentially confounding the results. The presence of cardiovascular disease, pulmonary diseases, smoking, alcoholism, gastric acid-suppressing drugs, and oral glucocorticoids was significantly higher in the statin group than the control group. These patients may have received more attentive care due to their multiple comorbidities and thus had better outcomes.

Another retrospective cohort study took these results further and evaluated, at two hospitals, 787 patients who had a diagnosis of community-acquired pneumonia. The study examined the effect of previous outpatient use of statins on mortality. Patients were included if they were older than 18 years, had an admission diagnosis of community-acquired pneumonia, and had a radiographically confirmed infiltrate or other finding consistent with community-acquired pneumonia on chest radiograph or computed tomographic scan obtained within 24 hours of admission. The pneumonia severity index score was used to assess severity of illness at presentation. The average age was 60 years, 79% were men, and 20% were admitted to the ICU. Mortality rate was 9.2% at 30 days and 13.6% at 90 days. Based on the pneumonia severity index, 52% were low risk, 34% were moderate risk, and 14% were high risk. A total of 110 subjects (14%) were taking statins at presentation. The authors found that in the multivariate regression analysis, after adjusting for potential confounders including a propensity score, the use of statins at presentation was associated with a decreased 30-day mortality rate (OR 0.36, 95% CI 0.14–0.92).

This study was an important addition to the data provided in the above-mentioned study, as the authors provided a more detailed procedure for the diagnosis of pneumonia, as well as data on well-established steps to decrease mortality from this condition such as the timing and appropriateness of first-dose antibiotics. Patients receiving statin therapy were more likely to be older and have a diagnosis of diabetes mellitus, chronic heart failure, or stroke. This study, however, was limited by the lack of information regarding the type, dose, duration, and continuation of statin use. Also, no data were provided regarding compliance with previous statin therapy.

A retrospective, population-based, cohort study investigated the effect of early statin use on the occurrence of sepsis in 69,168 patients with...
cardiovascular disease who had been hospitalized for acute coronary syndromes, ischemic stroke, or revascularization. The average age was 74 years, and most patients (56%) were men. No significant differences were noted in baseline characteristics, including previous infections and comorbidities. Among 34,584 patients receiving statin therapy, the most common statin prescribed was atorvastatin (37%), followed by simvastatin (28%), pravastatin (21%), lovastatin (10%), fluvastatin (3%), and cerivastatin (2%). Mean follow-up was 2.2 years, with 551 patients admitted for sepsis in the statin group versus 667 in the control group. It was found that statin therapy that was started within 3 months of discharge was associated with significant reductions in severe sepsis (hazard ratio [HR] 0.83, 95% CI 0.70–0.97) and fatal sepsis (HR 0.75, 95% CI 0.61–0.93). The authors found no benefit associated with nonstatin lipid-lowering agents (HR 0.95, 95% CI 0.75–1.22). Although this study was limited by its retrospective design, it does support the theory that, in the cardiovascular population, the benefit of statins in the short term (<3 mo) may help prevent mortality through noncardiovascular causes, not lipid lowering, and that this benefit is unique to statin therapy.

A prospective observational cohort study was conducted to investigate the effect of statin therapy on septic shock. Patients with presumed or documented acute bacterial infections due to pneumonia, urinary tract infection, or cellulitis were included. A total of 361 patients were evaluated, 82 of whom were taking statins for at least 1 month before admission. The largest diagnostic group was those with pneumonia (177 patients [49.0%]), followed by urinary tract infection (140 patients [38.8%]) and cellulitis (44 patients [12.2%]). As might be expected, the patients receiving statin therapy had more chronic diseases, as evidenced by significantly higher rates of hypertension, chronic ischemic heart disease, diabetes, and chronic renal failure, as well as higher levels of total cholesterol, LDL, high-density lipoprotein cholesterol, triglycerides, and serum albumin. The most common statin used was simvastatin (70%), and the most common dose was 20 mg/day (65%).

Despite the differences in the statin and nonstatin groups, the patients with more comorbidities (the statin group) did not develop sepsis as often as those not receiving statins. Fifty-three patients (19%) in the nonstatin group developed severe sepsis compared with only two (2.4%) in the statin group (p<0.001). Antibiotic therapy was deemed appropriate based on conforming to established guidelines, and no significant difference was found between the two groups with regard to conformity (p=0.68). The researchers concluded that statin use for at least 1 month before admission resulted in an absolute risk reduction of 16.6% (19% vs 2.4%, p<0.001) in the occurrence of severe sepsis. Although not powered for detecting differences in the rate of mortality, the authors also found a notable, but nonsignificant, decrease in the 28-day mortality rate in those taking statins (8.6% vs 3.7%, p=0.14).

This study is limited in that it was a nonrandomized observational study with a primary end point of the development, not treatment, of sepsis. Therefore, it is primarily hypothesis generating and does not establish a direct effect. In addition, no information regarding the resumption of statin therapy on admission was reported, which could have affected results depending on the timing of sepsis development and the possible duration of statin effect. The patient population is also limited to what might be classified as a medical ICU population, and those with only bacteremia would not have met the eligibility criteria for this study, somewhat weakening its external validity. As one of the primary theories behind the efficacy of this therapy is its antiinflammatory effect, validity would have been gained from assessing inflammatory biomarker data, but the observational nature of the study did not allow this. Larger prospective, interventional studies need to be conducted to further confirm these results and allow the collection of inflammatory biomarker data, as well as timing of statin initiation and continuation.

Some recent data may actually suggest a negative impact of statin therapy in this setting. In a prospective cohort study, 3415 patients hospitalized with pneumonia were evaluated to determine if statin therapy had an effect on the composite end point of in-hospital mortality and admission to an ICU. Statin use was defined as receiving drug therapy at least 1 week before admission and continuing it during the hospital stay. A pneumonia severity index score was calculated for each patient to assist in stratification. Data were not collected on specific statins or dosages; however, 90% of the statins dispensed were simvastatin, pravastatin, and atorvastatin. The average patient age was 75 years, and 53% were men. Ten percent (325
Cerebral vasospasm constitutes one of the major complications associated with subarachnoid hemorrhage and is a significant contributor to the delayed morbidity and mortality associated with the event. Vasospasm occurs in up to 70% of those with an aneurysmal subarachnoid hemorrhage and causes symptomatic brain ischemia in approximately 36% of all patients. Despite the high frequency and devastating sequelae associated with this event, it remains unclear how exactly the presence of subarachnoid blood causes the delayed vasoconstriction of the cerebral arteries. One proposed mechanism is the involvement of inflammatory processes in this vasoconstriction. Other potential mechanisms of vasospasm are the increased production of superoxide anions and iron ions after hemolysis, which leads not only to elevated levels of reactive oxygen species but also to increased binding of nitric oxide. Animal models have confirmed the potential benefit of statins as evidenced by attenuation of cerebral vasospasm and neurologic deficits with 14 days of pretreatment with simvastatin. Increasing research in humans to investigate the statin effects in preventing vasospasm has yielded promising results. A matched, controlled, prospective cohort study was conducted to investigate the statin effects in preventing vasospasm and neurologic deficits with 14 days of pretreatment with simvastatin. The study had impressive results, specific statin therapies, dosages, duration of therapy, continuation of therapy on admission, and underlying comorbidities were not reported, making the results of this study difficult to interpret.

A matched, controlled, prospective cohort study was conducted to investigate the hypothesis that previous statin use would be beneficial in improving 14-day functional outcome and prevent vasospasm-induced delayed cerebral ischemia or stroke during hospitalization for aneurysmal subarachnoid hemorrhage. Of 624 consecutive patients with subarachnoid hemorrhage, 20 statin users were matched with 40 nonstatin users based on cardiovascular disease, age, and subarachnoid hemorrhage severity. Functional condition was assessed by using the Modified Rankin Scale (MRS), Barthel...
The primary end points were the controlled trials. and lay the groundwork for larger randomized
serves to further stimulate interest in this area
significant difference is impressive. This study appeared to use the best available criteria
regard to this, and other studies for this indication, is the intricacy and complexity of
investigate the effects of newly initiated statin therapy for this indication. The difficulty with
occur only after the 14-day trial had been completed, possibly lending credence to the
negative impact of statin withdrawal in patients or perhaps the occurrence of late vasospasm.

Although baseline data are somewhat lacking, this study is one of the first to prospectively
The activity of statins in subarachnoid hemorrhage was tested in a phase II, randomized,
placebo-controlled trial of 80 patients with aneurysmal subarachnoid hemorrhage who were
randomly assigned to receive either oral pravastatin 40 mg/day or placebo daily for up to
14 days. The primary end points were the occurrence, duration, and severity of cerebral
vasospasm, and the duration of impaired autoregulation estimated by TCD. Secondary
end points included the occurrence of vasospasm-related delayed ischemic neurologic
deficits and disability at discharge. Patients receiving previous statin therapy were excluded
from this study. Statin therapy was started within 1.8 days of the initial insult. Thirty-eight
patients completed the total of 14 days of statin therapy. Two patients had early withdrawal of
statin therapy; however, all 80 patients were included in the final analysis. No data regarding
baseline comorbidities, concomitant drugs, or lipid profiles were reported. The authors found
32% and 42% of patients receiving pravastatin had reduced rates of vasospasm and severe
vasospasm on TCD, respectively (p=0.006 and p=0.044), compared with placebo. These effects
appear to be largely attributable to significant differences found in ipsilateral measurements
that were not present on the contralateral side. A nonsignificant reduction in the duration of severe
vasospasm was noted by 0.7 day (p=0.068). Also, a significant reduction was noted in the
period of impaired cerebral autoregulation on both ipsilateral and contralateral sides (p=0.011
and p=0.008, respectively). Compared with placebo, pravastatin significantly reduced
vasospasm-related delayed ischemic deficits (30% vs 5%, p<0.001) and mortality (20% vs 5%,
p=0.037). Of interest, the delayed ischemic neurologic deficits in the pravastatin group occurred
only after the 14-day trial had been completed, possibly lending credence to the negative impact of statin withdrawal in patients or perhaps the occurrence of late vasospasm.

Although baseline data are somewhat lacking, this study is one of the first to prospectively
investigate the effects of newly initiated statin therapy for this indication. The difficulty with
regard to this, and other studies for this indication, is the intricacy and complexity of
identifying cerebral vasospasm; however, this study appeared to use the best available criteria
for the analysis. The authors report that standard triple-H therapy was used along with nimodipine,
per specific department protocol. Differences in

Delayed cerebral ischemia was defined as delayed clinical neurologic deterioration that could not be
attributed to any other cause. Delayed vasospasm was defined as TCD highest mean velocity greater than 120 cm/second or a change from baseline of 50 cm/second or greater. At baseline, there were significantly more patients with hypercholesterolemia in the statin group; however, no differences were noted between the groups with regard to aneurysmal location, size, or type of aneurysmal treatment.

Statin users had a significantly improved functional outcome at 14 days from the onset of subarachnoid hemorrhage compared with nonusers. Statin users had a significantly higher Barthel Index score (77 vs 39, p=0.003) and a significantly lower Lawton Physical Self-Maintenance Scale score (12 vs 19, p=0.03). Using the same variables, the authors also noted an apparent increased effect in those patients with a Hunt and Hess score of 3 or greater at admission for the above functional outcome variables. In terms of secondary outcomes, no significant difference was noted between the two groups with regard to 14-day mortality (p=0.46).

Of interest, patients taking statins did have lower TCD highest mean velocity values (102 vs 139 cm/sec, p=0.05), as well as lower rates of delayed cerebral ischemia (10% vs 43%, p=0.02), delayed cerebral ischemia confirmed by angiography and/or TCD (5% vs 35%, p=0.01), and cerebral infarcts (25% vs 63%, p=0.01) during their hospitalization. The statin group also had significantly fewer patients with TCD highest mean velocity changes of 50 cm/second or greater (18% vs 51%, p=0.03).

As is the case with many of these studies, a major flaw is the lack of information detailing the duration of therapy before admission, as well as the sparcity of information regarding its continuation on admission. Further confounding these results is the fact that the authors report that 64% of previous statin users continued their statin treatment, and 11% of the control group started to receive statins during their admission. Also, no data detailing the type of statin used and dosage were reported. The small patient numbers largely limit these results; however, the fact that the authors were still able to denote a significant difference is impressive. This study serves to further stimulate interest in this area and lay the groundwork for larger randomized controlled trials.
the rates of vasospasm between the contralateral and ipsilateral sides may or may not be significant and may provide a basis for a more specific vasospastic effect of statin therapy. Both the use of pravastatin and a dose of 40 mg appear to have been a relatively arbitrary determination, and these results may or may not be extrapolatable to other statins. It is unknown if the increased lipophilicity of other statins such as simvastatin and atorvastatin will enhance the stabilization of cerebrovascular tone.74

A smaller, randomized trial investigated the effects of simvastatin 80 mg/day or placebo in 39 patients who came to the hospital within 48 hours of aneurysmal subarachnoid hemorrhage.57 The occurrence of cerebral vasospasm was found to be significantly lower in the group receiving simvastatin (5 vs 12 patients, p<0.05) as was the maximum mean middle cerebral artery TCD velocity compared with the placebo group (103 vs 149 cm/sec, p<0.01).

The above studies demonstrate significant alterations in both radiographic and functional outcomes in patients with subarachnoid hemorrhage. Although the designs, end points, and choice of statin vary among these investigations, all denoted an approximate 30% decrease in the rates of vasospasm and clinical sequelae associated with subarachnoid hemorrhage. Together, these studies provide encouraging data for further investigation into the potential utility of statins for this indication.

Some literature has actually suggested, however, that a negative impact of statin therapy may exist with regard to cerebral vasospasm. In a retrospective review of data from 514 patients with subarachnoid hemorrhage, the authors attempted to define risks for vasospasm, symptomatic vasospasm, and poor clinical outcomes in patients using calcium channel blockers, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, aspirin, selective serotonin reuptake inhibitors (SSRIs), non-SSRI vasoactive antidepressants, or statins before their event.58 Vasospasm was considered present based on the results of direct or indirect angiography or TCD studies. Poor clinical outcome was assessed by using the discharge MRS score. Symptomatic vasospasm was defined as a focal neurologic deficit or neurologic worsening unrelated to other causes. The average age was 55 years, and 71% of patients were women. Vasospasm was documented in 62% of patients, 29% of whom developed symptomatic vasospasm. Thirty-six patients were receiving statin therapy: atorvastatin (23 patients), simvastatin (5), pravastatin (4), lovastatin (2), and fluvastatin (2). In 19 of these patients, statin therapy was discontinued after admission. Statin users were found to be at a higher risk of vasospasm (OR 2.25, 95% CI 0.97–5.83, p=0.05) but not symptomatic vasospasm (OR 1.62, 95% CI 0.74–3.41, p=0.18). Among those in whom statin therapy was discontinued, the risk of vasospasm was nonsignificantly higher (OR 2.35, 95% CI 0.74–9.88, p=0.15) as was symptomatic vasospasm (OR 2.28, 95% CI 0.8–6.34, p=0.12). Statin therapy had a nonsignificant impact on poor clinical outcomes measured by MRS score (OR 1.06, 95% 0.45–2.5).

This is the first study, to our knowledge, to document an increased risk of vasospasm in those treated with statin therapy. Despite the relatively large number of patients (514 patients) in the study, relatively few were receiving statin therapy (36 patients). Although the types of statins are reported, the actual dosages and duration of therapy before admission are not. It is interesting that the authors analyzed the effects of statin withdrawal in this population, as abrupt cessation may result in a rebound effect of statin-modified processes. Although this analysis did not reach statistical significance, it did deplete the already low numbers of patients in the statin group, making analysis of these results difficult. As the data are not reported, it is unclear if there existed baseline disparities in terms of underlying diseases typically associated with statin users in the statin group compared with nonusers. Despite these concerns, it does highlight the fact that more research needs to be conducted in this area to fully delineate the effects statins have in the acute setting.

Ischemic Stroke

Research indicating possible effects of statin therapy on the endothelium and potential fibrinolytic effects beyond the agents’ lipid-lowering activity has led to investigations into the use of these agents in the acute setting of stroke.10, 35, 71 The mechanism has been a proposed upregulation of eNOS, leading to improved cerebral blood flow.75, 76 High-dose atorvastatin 80 mg/day has been shown to decrease the rate of recurrent stroke or transient ischemic attack in patients with no known history of coronary artery disease. When therapy was started within 1–6 months of the initial event, the 5-year rate of recurrent stroke was
Further analysis of these results is necessary to delineate whether this effect is attributable to lipid-lowering effects alone. A larger cardiovascular study examining the effects of high-dose atorvastatin versus placebo started within 24–96 hours after admission for unstable angina or non–Q-wave acute myocardial infarction also found a decrease in the rate of stroke at 16 weeks (12 vs 24 patients, p=0.045), further supporting this theory. A MEDLINE-PubMed search (1966–January 2007) was conducted combining the terms “statins” and “stroke” for the identification of primary research studies. Articles were excluded if they were conducted in animals or if the articles were not in English. The studies evaluating statins in ischemic stroke are summarized in Table 1.

The impact of previous statin therapy on 143 patients with acute unilateral nonlacunar middle cerebral artery territory ischemic strokes on magnetic resonance images less than 48 hours from symptom onset was retrospectively reviewed. A total of 38 patients reported taking a statin at the time of their stroke, including 24 taking atorvastatin (median dose 20 mg/day), 10 taking simvastatin (median dose 20 mg/day), 3 taking pravastatin (median dose 40 mg/day), and 1 taking lovastatin 20 mg/day. The statin group had significantly more patients with hyperlipidemia, atrial fibrillation, and coronary artery disease and more patients taking ACE inhibitors, aspirin, antiplatelets, and warfarin. Statin users were also more likely to have cardioembolic or large-vessel atherothromboembolic strokes compared with the nonstatin group. Patients taking statins had a tendency toward smaller infarct volume on univariate analysis (median 15.5 vs 25.4 cm³, p=0.054). The authors concluded that statin therapy was associated with a reduction in diffusion-weighted imaging volume of 42% (95% CI 5–66%).

This study is distinctive in that it reports not only the specific statin therapy but also the median doses; nevertheless, the individual numbers were too small to provide adequate analysis. It is encouraging, however, that none of those doses were at recommended maximums, leaving open the question of increased benefit if such doses were applied. Although this is a positive trend, it should be noted that the results were nonsignificant and that the patients in the statin group, while having more comorbidities, were also more likely to be receiving therapies to decrease the risk of stroke (i.e., aspirin, warfarin, etc.). These issues greatly impair the analysis of these results.

In a retrospective study of data from consecutive patients with ischemic stroke who were admitted to an acute-stroke unit, patients who reported a history of statin use 1 month before admission (205 patients) were each matched with two nonusers (410 patients). Stroke outcome was assessed from mortality rates at 1 month and during follow-up. Patients in the statin group were significantly younger, had lower blood pressure, and had more hyperlipidemia, previous strokes, previous myocardial infarctions, and angina. After adjusting for multiple factors (age, hyperlipidemia, peripheral vascular disease, stroke, myocardial infarction, angina, stroke subtype, baseline National Institutes of Health Stroke Scale [NIHSS] score, blood pressure), statin use was associated with reduced mortality at 1 month (OR 0.24, 95% CI 0.09–0.67) and during a mean 2.4-year follow-up (HR 0.57, 95% CI 0.35–0.93).

This is the only study we found that correlates statin therapy in the setting of stroke with decreased mortality rate. However, the application of these results is significantly impaired by the lack of data regarding the type and dosage of the statins used to produce this effect, as well as the duration and compliance with this therapy before admission. Also, no data were available regarding the continuation or discontinuation of this therapy on admission. Obvious limitations exist with this study design that are evident in the differences in baseline characteristics reported, as well as the omission of reporting other concomitant drugs such as aspirin, antiplatelet therapies, and warfarin for stroke protection. Also notably absent are data regarding functional outcome in these patients.

To assess the effects of statin therapy on outcome after acute stroke, case report forms from the phase III citicoline trial were reviewed. Patients were divided into groups based on whether they received statins before stroke, after stroke onset, or never received a statin. Patients taking citicoline (a form of the essential nutrient choline being investigated for its potential to decrease infarct volume in the setting of stroke) were equally distributed between the groups. A total of 129 patients were receiving statins before the event, 123 patients had statins started within 4 weeks, and 600 patients were not receiving statins. Favorable outcome was defined as an NIHSS score of 2 or less and an MRS score of 2 or
less at 12 weeks. Any statin therapy was found to be a significant predictor of good outcome (OR 1.07, 95% CI 0.69–1.66, p=0.008) as measured by NIHSS score, as well as by MRS score (OR 1.03, 95% CI 0.54–1.27, p=0.045). Of interest, therapy started after stroke was associated with a significant probability of a favorable outcome as measured by NIHSS and MRS scores (p=0.002 and 0.033, respectively). Prestroke statin therapy was associated with nonsignificant trends in benefit as measured by NIHSS and MRS scores (p=0.07 and 0.08, respectively).

The results of this study highlight the potential complexity of the issue. Although the reason behind the difference in results obtained between the two statin groups is not obvious, the authors propose the possible existence of a saturation effect with regard to the beneficial effects of statins. The substudy nature of this study and the small patient numbers do limit the applicability of these findings. These data are further clouded by the use of various statins and dosages during the original study. Also, no data are available regarding the duration of therapy before stroke in the statin group or on the exact timing of the initiation of statin therapy beyond the first 4 weeks. One would contend that if the effects of statins were due to their short-term changes, then the timing of their initiation surrounding stroke would be valuable information. Nevertheless, these data do provide evidence of yet another possible role for statins, but they also complicate the issue by suggesting that these effects may be primarily short term and could diminish or be less effective over time.

Discussion

Data continue to emerge demonstrating various effects of statins that go beyond their initial indication. These pleiotropic effects may extend from anti-inflammatory to immunomodulatory to effects on vascular tone and may very likely have clinical relevance. Most of the published human studies are observational and retrospective, with the exception of those on cerebral vasospasm prevention. Although some of the available data are circumstantial, it is nevertheless compelling. The use of what has become a routine drug in our society to combat illnesses that have few effective therapeutic options, like sepsis and cerebral vasospasm, would be a significant advance. The total number of patients assessed in the setting of sepsis in the six studies reviewed is 35,446, showing benefits in five of the studies.46–53 A potential reduction in the relative risk of mortality from sepsis by 16.6% compares favorably with some of most significant advancements in ICU care, such as early goal-directed therapy and drotrecogin alfa (activated)79,80 These effects, however, must also be appropriately weighed against the potential harm suggested by the results of three studies.47,53,58

Also of concern is the impact that abrupt withdrawal of these drugs may be having on patient outcomes. Further investigation into the withdrawal of statin therapy needs to be pursued, as cessation of therapy has been shown to rapidly (2–4 days) result in a loss of protection against cerebral ischemia and thrombus formation in a murine model.39 One group of authors demonstrated that such withdrawal may result in increased mortality from bacteremia, as statin continuation significantly reduced mortality (OR 0.058, 95% CI 0.008–0.43).44 Results from another study also indicate that statin withdrawal may affect the occurrence of vasospasm, demonstrating an observational increase in delayed ischemic neurologic deficits after only 14 days of pravastatin 40 mg/day in previously statin-naïve patients.56 These data suggest that abrupt cessation of statin therapy might be of clinical concern and can have a negative impact. Further elucidation of this phenomenon and its clinical relevance may greatly alter how prescribers and pharmacists view home drug therapy reconciliation when patients are admitted to an acute care environment and change how pharmacists educate patients and physicians about statin therapy.

Several questions remain regarding the utilization of statins as a therapy in acute situations such as sepsis and stroke. Beyond the necessary randomized clinical trials to firmly establish statins as efficacious, it is necessary to determine if the pharmacokinetic nuances among statins affect the pleiotropism in various tissues or if the pleiotropic effects are a class effect in all tissues. One group of authors found that some statins can have differing cellular effects, raising the question of whether one statin may be superior to the others.81 The available literature makes such an analysis impossible. When actual therapy is reported, the literature reflects the use of several statins, largely due to the retrospective nature of most of these trials. The most common statin in studies of bacteremia has been simvastatin (174 of 315 patients), in sepsis it has been atorvastatin (12,855 of 35,446), in vasospasm it has been pravastatin (44 of 130), and in ischemic stroke it
has been atorvastatin (24 of 495). Also, the precise effect of the duration of therapy before admission on the event outcome is unknown.

The results of the citocoline trial substudy analysis point out that there may be a difference in efficacy based on the timing of statin initiation, and the cause of these results needs to be explored if this is to become a standard of care.

Conclusion

At this time, the data do not warrant routine statin initiation in the acute setting of bacteremia, sepsis, aneurysmal subarachnoid hemorrhage, or ischemic stroke. Further prospective studies need to be conducted to firmly establish the true effects statins may have in these acute processes. In contrast, the data do seem to indicate that abrupt cessation of these agents, particularly in acutely ill individuals, may increase the risk of adverse consequences; therefore, unless harm will be done by continuing therapy, it seems prudent for health care providers to take an active role in restarting or continuing these drugs.

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