Statin Use Following Intracerebral Hemorrhage

A Decision Analysis

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Context: Statins are widely prescribed for primary and secondary prevention of ischemic cardiac and cerebrovascular disease. Although serious adverse effects are uncommon, results from a recent clinical trial suggested increased risk of intracerebral hemorrhage (ICH) associated with statin use. For patients with baseline elevated risk of ICH, it is not known whether this potential adverse effect offsets the cardiovascular and cerebrovascular benefits.

Objective: To address the following clinical question: Given a history of prior ICH, should statin therapy be avoided?

Design: A Markov decision model was used to evaluate the risks and benefits of statin therapy in patients with prior ICH.

Main Outcome Measure: Life expectancy, measured as quality-adjusted life-years. We investigated how statin use affects this outcome measure while varying a range of clinical parameters, including hemorrhage location (deep vs lobar), ischemic cardiac and cerebrovascular risks, and magnitude of ICH risk associated with statins.

Results: Avoiding statins was favored over a wide range of values for many clinical parameters, particularly in survivors of lobar ICH who are at highest risk of ICH recurrence. In survivors of lobar ICH without prior cardiovascular events, avoiding statins yielded a life expectancy gain of 2.2 quality-adjusted life-years compared with statin use. This net benefit persisted even at the lower 95% confidence interval of the relative risk of statin-associated ICH. In patients with lobar ICH who had prior cardiovascular events, the annual recurrence risk of myocardial infarction would have to exceed 90% to favor statin therapy. Avoiding statin therapy was also favored, although by a smaller margin, in both primary and secondary prevention settings for survivors of deep ICH.

Conclusions: Avoiding statins should be considered for patients with a history of ICH, particularly those cases with a lobar location.


Although the benefits of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for reducing risk of cardiac and cerebrovascular disease are well established,1,2 more widespread use of statin therapy remains controversial. A particular subgroup of patients for whom the advisability of statin use is unclear are those at high risk for intracerebral hemorrhage (ICH).3 The reason for added concern is the increased incidence of ICH observed among subjects randomized to statin therapy in a clinical trial of secondary stroke prevention.2,4 This risk amplification might have greatest relevance to patients at high risk for hemorrhage by virtue of prior ICH, particularly hemorrhages in lobar brain regions characteristic of the degenerative vascular condition cerebral amyloid angiopathy.5,6 Because ICH survivors commonly have co-morbid cardiovascular risk factors that would otherwise warrant cholesterol-lowering medication, it is important to weigh the risks and benefits of statin therapy in this population.

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Given the uncertainty surrounding this clinical decision, we developed a decision analytic model.7 Decision analytic models have been applied to the clinical issue of anticoagulation in patients with a high risk of falling8 or a history of ICH,9 and to the cost-effectiveness of statin therapy in coronary and cerebrovascular disease.10,11 To provide guidance for the frequently encountered question of whether statin use is safe after ICH, we used a decision analytic model incorporating published data regarding the beneficial effects of...
Simulated clinical trials were conducted with a Markov state transition model implementation in Matlab (The Mathworks, Natick, Massachusetts). The base case for these analyses is a 65-year-old male ICH survivor. The impact of statin therapy vs no statin therapy was considered under 3 basic scenarios involving differing risk for future cerebrocardiovascular events: (1) no prior cerebral ischemic event (transient ischemic attack or ischemic stroke) and no prior cardiac ischemic event (angina or MI); (2) prior ischemic stroke at least 1 year in the past (hereafter referred to as prior stroke); and (3) prior MI at least 1 year in the past. For the risk of stable and unstable angina, a prior MI signifies that, in the model, lower risk health states are not accessible after an MI.

Table 1. Base-Case Event Risks, Relative Risks, and Quality-of-Life Adjustment Factors

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk in Primary Prevention</th>
<th>Risk in Secondary Prevention</th>
<th>RR on Statin Therapy</th>
<th>QALYs off Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable angina</td>
<td>4.8</td>
<td>NA</td>
<td>0.59</td>
<td>0.81</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.8</td>
<td>NA</td>
<td>0.72</td>
<td>0.77</td>
</tr>
<tr>
<td>Nonlethal MI</td>
<td>3.8</td>
<td>18.5</td>
<td>0.66</td>
<td>0.76</td>
</tr>
<tr>
<td>Lethal MI</td>
<td>2.1</td>
<td>15.2</td>
<td>0.74</td>
<td>0.70</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2.2</td>
<td>2.2</td>
<td>0.79</td>
<td>1.00</td>
</tr>
<tr>
<td>Nonlethal stroke</td>
<td>6.0</td>
<td>2.2</td>
<td>0.77</td>
<td>0.63</td>
</tr>
<tr>
<td>Lethal stroke</td>
<td>1.4</td>
<td>1.4</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Nonlethal lobar ICH</td>
<td>113.4</td>
<td>113.4</td>
<td>1.68</td>
<td>0.47</td>
</tr>
<tr>
<td>Lethal lobar ICH</td>
<td>26.6</td>
<td>26.6</td>
<td>1.68</td>
<td>0.60</td>
</tr>
<tr>
<td>Nonlethal deep ICH</td>
<td>16.7</td>
<td>16.7</td>
<td>1.68</td>
<td>0.45</td>
</tr>
<tr>
<td>Lethal deep ICH</td>
<td>4.3</td>
<td>4.3</td>
<td>1.68</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Abbreviations: ICH, intracerebral hemorrhage; MI, myocardial infarction; NA, not accessible; Q, quality of life adjustment factor; RR, relative risk.

Methods:

We simulated the effect of statins on quality-adjusted life expectancy (ie, QALYs) for patients with a history of lobar ICH separately from its effect on QALYs for patients with a prior deep ICH. Table 1 lists the base-case values used for these analyses, and the eTable lists the transition probabilities and quality-of-life values for the individual states. The increased risk of ICH associated with statin therapy (RR, 1.68) was taken from the SPARCL study.

Results:

Our base-case patient was a 65-year-old man with lobar ICH and a 20% risk of cerebrocardiovascular disease (CVD) in the following 10 years. In the primary prevention setting (ie, no prior history of ischemic cerebrovascular or cardiac events), avoiding statins was the preferred choice. This option resulted in the accrual of 6.8 QALYs, whereas statin therapy resulted in the accrual of 4.6 QALYs, a net loss for statin use of 2.2 QALYs. Modeling of statin therapy under various secondary prevention scenarios also suggested a net benefit for avoiding statins. Predicted outcomes in the setting of a history of prior MI were 4.4 QALYs on statin therapy vs 6.2 QALYs off statin therapy; for history of prior ischemic stroke, the figures were 4.2 vs 6.0 QALYs, respectively.

In sensitivity analyses, avoiding statins remained the preferred option following lobar ICH over a wide range of values for the statin-associated RR of ICH (Table 2, Figure 1). Even at the lower limit of the 95% confidence interval, 1.09-2.59; this risk was assumed to apply to nonlethal lobar ICH separately from its effect on QALYs for patients with a prior deep ICH. Table 1 lists the base-case values used for these analyses, and the eTable lists the transition probabilities and quality-of-life values for the individual states. The increased risk of ICH associated with statin therapy (RR, 1.68) was taken from the SPARCL study.

Abbreviations: CVD, cerebrocardiovascular disease; ICH, intracerebral hemorrhage; MI, myocardial infarction; NP, never preferred.

a Base-case annual recurrence rate for lobar ICH, 14%/year; for deep ICH, 1.7%/year.
b Statins never preferred. For RR of ICH thresholds, 10-year CVD probability was set to 20%. For 10-year CVD probability thresholds, RR of ICH was set to 1.68.
Figure 1. Sensitivity analyses for lobar intracerebral hemorrhage (ICH) in the primary prevention (left) and prior myocardial infarction (MI) (right) settings. Plots show quality-adjusted life-years (QALYs) off statin therapy (dashed line) and on statin therapy (solid line), as a function of the 10-year cerebrocardiovascular disease (CVD) event probability (CVD10) (A); the annual MI recurrence probability expressed as multiples of the base-case probability (Base-Case Probability MI) (E); the relative risk (RR) of ICH conferred by statin therapy (RR ICH on Statin) (B and F); and off-statin ICH annual recurrence probability [ICH Probability (Off Statin)] (C and G). Two-dimensional sensitivity analyses varying RR of ICH on statin vs CVD10 in primary prevention (D) and RR ICH vs base-case MI recurrence probability in secondary prevention (H) are also shown. For these plots, the third dimension (gray-scale gradient) depicts the QALYs on statin minus QALYs off statin, allowing one to see when the net difference is positive (favor statin continuation) vs negative (favor statin discontinuation). Clinical circumstances in which the QALY difference is negative are shown to the right of the thick decision boundary line, whereas net positive QALY differences are shown to the left of this decision boundary line. Base-case values are marked with white circles. Q indicates the quality-of-life adjustment factor.
interval of the RR for ICH reported in the SPARCL study (ie, 1.09), avoiding statins remained the preferred option by a small margin (net loss for statin use of 0.3 QALYs). For statin therapy to be favored, the RR of ICH would need to be less than or equal to 1.03 for primary prevention, 1.07 for secondary prevention after MI, and 1.06 for secondary prevention after ischemic stroke.

In complementary sensitivity analyses, we found the strategy of avoiding statins following lobar ICH to be robust to other values used in the base-case model as well. Avoiding statins remained the preferred strategy at (off-statin) annual ICH recurrence probabilities well below the base-case value of 14% per year (Table 2). Avoiding statins was also preferred over the entire range of 10-year CVD risk values considered (0%-80%) for primary prevention, and for risks of MI recurrence up to 6-fold greater than the base-case assumption for secondary prevention (Figure 1E). These results indicate that the risk of ICH on statin therapy is not offset by the secondary prevention benefits, even if the cardiovascular risks are artificially forced to be extremely high. Two-way sensitivity analyses varying both the RR of ICH and the 10-year CVD risk (for primary prevention; Figure 1D) or MI recurrence probability (for secondary prevention; Figure 1H) again demonstrate that avoiding statins is preferred through a wide range of values around the base-case assumptions.

DEEP ICH

We performed similar analyses for our other base-case patient, a 65-year-old man with a 10-year CVD risk of 20% at the time of a deep ICH. In this scenario, the risk of recurrent ICH is substantially lower. Assuming the 1.68 RR of ICH from the SPARCL data, in the primary prevention setting, statin therapy confers a net loss of 0.8 QALYs (13.0 vs 12.2 QALYs) (Table 3). In the secondary prevention settings, statin therapy also produced net QALY losses, although they were smaller (0.2 QALYs for the post-MI setting and 0.3 QALYs for the post—ischemic stroke setting).

Thresholds for the statin-associated RR of ICH below which statin therapy was preferred were 1.20 for primary prevention, 1.50 for secondary prevention after MI, and 1.41 for secondary prevention after ischemic stroke (Table 2 and Figure 2B and F). The off-drug probabilities for ICH recurrence at which statin therapy was preferred also came relatively close to the base-case value (2.1%), including the secondary prevention settings of prior MI (1.5%) or ischemic stroke (1.3%) (Table 2). In the post-MI scenario, statin therapy was preferred if the probability of MI increased to 1.4 times the base-case probability (Table 2). Decision boundaries from a 2-way sensitivity analysis of RR for ICH and 10-year CVD risk in the primary prevention setting and of RR for ICH and MI recurrence probability in the post-MI setting for deep ICH are shown in Figure 2D and 2H, respectively.

The differences in QALYs for the various scenarios discussed emerge from interactions among multiple competing factors during a patient’s life span. It is also instructive to consider the effect of individual factors over shorter time spans. Using the base-case assumptions and measuring over a single year of follow-up, primary prevention with statin therapy is projected to prevent fewer than 2 deaths from either MI or ischemic stroke per 1000 patients per year, at the expense of causing 18 lobar ICHs (in patients with prior lobar ICH) or 3 deep ICHs (in patients with prior deep ICH) per 1000 patients per year. From the perspective of disability and resulting loss of quality of life, each year of primary prevention with statin treatment saves 2.6 QALYs from MI or 2.2 QALYs from ischemic stroke per 1000 patients per year, at the expense of 58.6 QALYs for lobar ICH or 9 QALYs for deep ICH.

We used a decision analytic model to evaluate a common dilemma facing physicians of patients with a history of prior ICH and indications for statin therapy: under what clinical circumstances should statin therapy be avoided because of risk of recurrent ICH? Our analysis indicates that in settings of high recurrent ICH risk, avoiding statin therapy may be preferred. For lobar ICH in particular, which has a substantially higher recurrence rate than does deep ICH, statin therapy is predicted to increase the baseline annual probability of recurrence from approximately 14% to approximately 22%, offsetting the cardiovascular benefits for both primary and secondary cardiovascular prevention. Our results were robust over a wide range of CVD event rates in both primary and secondary prevention settings and over a wide range of estimates for the statin-associated RR of ICH.

In the case of deep ICH, the substantially lower baseline annual recurrence rate translates into a much closer balance between statins’ risks and benefits, and consequently the optimal treatment option may vary with specific circumstances. For our base-case patient with deep ICH, we found that statin therapy was worse than no treatment, but this conclusion is sensitive to variations in the assumed baseline recurrence rates of ischemic events and ICH, and the statin-associated RR of ICH, such that, in some realistic secondary prevention settings, statin therapy may be preferred.

The different results for statin use after lobar vs deep ICH arise primarily from the different annual ICH recurrence probabilities in these 2 groups. These 2 ICH

<table>
<thead>
<tr>
<th>Table 3. Results of Base-Case Decision Analysis</th>
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<tbody>
<tr>
<td>Prior ICH Location and Setting</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Lobar ICH</td>
</tr>
<tr>
<td>Primary prevention</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
</tr>
<tr>
<td>Prior ischemic stroke</td>
</tr>
<tr>
<td>Deep ICH</td>
</tr>
<tr>
<td>Primary prevention</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
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<tr>
<td>Prior ischemic stroke</td>
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</tbody>
</table>

aAssuming a relative risk of 1.68 for intracerebral hemorrhage (ICH).
Figure 2. Sensitivity analyses for deep intracerebral hemorrhage (ICH) in the primary prevention (left) and prior myocardial infarction (MI) (right) settings. Plots show quality-adjusted life-years (QALYs) off statin therapy (dashed line) and on statin therapy (solid line), as a function of the 10-year cerebrocardiovascular disease (CVD) event probability (CVD10) (A); the annual MI recurrence probability expressed as multiples of the base-case probability (Base-Case Probability MI) (E); the relative risk (RR) of ICH conferred by statin therapy (RR ICH on Statin) (B and F); and off-statin ICH annual recurrence probability [ICH Probability (Off Statin)] (C and G). Two-dimensional sensitivity analyses varying RR of ICH on statin vs CVD10 in primary prevention (D) and RR ICH vs base-case MI recurrence probability in secondary prevention (H) are also shown. For these plots, the third dimension (gray-scale gradient) depicts the QALYs on statin minus QALYs off statin, allowing one to see when the net difference is positive (favor statin continuation) vs negative (favor statin discontinuation). Clinical circumstances in which the QALY difference is negative are shown to the right of the thick decision boundary line, whereas net positive QALY differences are shown to the left of this decision boundary line. Base-case values are marked with white circles. Q indicates the quality-of-life adjustment factor.
locations appear to reflect different underlying pathophysiology, nontraumatic lobar ICH in the age range under consideration is mostly due to cerebral amyloid angiopathy, whereas hypertensive vascular disease is primarily responsible for deep ICH. The risk of recurrent deep ICH can be lowered by the use of appropriate antihypertensive medical therapy, whereas cerebral amyloid angiopathy currently lacks an established preventive treatment. Patients with cerebral amyloid angiopathy are at risk for symptomatic ICH and for accumulation of clinically silent microhemorrhages, which may serve as the substrate for subsequent larger ICH events, explaining the observed continued risk of lobar ICH over the course of a lifetime.

The mechanism by which statins might amplify the risk of hemorrhagic stroke remains unclear. Historically, concerns about increased ICH risk with lipid-lowering drug therapy have centered on epidemiological studies linking low cholesterol levels with an increased rate of hemorrhagic stroke. This apparent association may be weaker than originally thought, and the increased risk of ICH with statin therapy found in the SPARCL study was independent of low-density lipoprotein levels. Statins are known to have pleiotropic effects, independent of their effect on cholesterol levels, and some of these have been proposed as possible mechanisms for increasing ICH risk. For example, there is evidence that statins may have antithrombotic and fibrinolytic effects, and may enhance the activity of other fibrinolytic agents. The dose and statin-type dependency of these effects is not yet well understood.

There are important limitations to this analysis. The data driving the statin-related RR of ICH derive from post hoc analysis of a single clinical trial, performed for ischemic and hemorrhagic stroke patients randomized to receive a single dose and statin agent (80 mg of atorvastatin calcium). It is therefore uncertain whether these results generalize across multiple populations, agents, and doses. A further potential limitation of our study is that we restricted our analysis to simple all-or-none strategies of either treatment or nontreatment. It is possible, however, that a "switch-over" strategy (eg, treating a patient with statins during the early high-risk period following MI or stroke followed by cessation of treatment) might be preferable. Despite these limitations, it is notable that the finding of net loss of QALYs in statin treatment of patients with lobar ICH persisted even at the lower 95% confidence limit observed in the SPARCL study, supporting its validity. A second major limitation that applies to all decision analyses is their reliance on parameters extracted from existing literature, which may contain uncertainties. Although only a randomized trial could definitively answer the questions raised in our study, we note that the sensitivity analyses performed to address some of this uncertainty support our fundamental findings. Another important caveat is the possibility (identified in some but not all observational studies) that patients on statin therapy at the time of ICH have better outcomes than those not on statin therapy. Although such statin-associated improvements in ICH outcome would partially mitigate the loss of QALYs associated with increased ICH incidence, they appear insufficient to significantly offset this effect in patients with lobar ICH in our model (data not shown).

In summary, mathematical decision analysis of the available data suggests that, because of the high risk of recurrent ICH in survivors of prior hemorrhagic stroke, even a small amplification of this risk by use of statins suffices to recommend that they be avoided after ICH. In the absence of data from a randomized clinical trial (ideally comparing various agents and doses), the current model provides some guidance for clinicians facing this difficult decision.

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Online-Only Material: The eAppendix, eTable, and eFigure are available at http://www.archneurol.com.

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REFERENCES


