A 78-year-old male patient arrives at the emergency department 3 hours after sudden onset of aphasia and right-sided sensorimotor hemiparesis (National Institutes of Health Stroke Scale=8). There is a medical history of coronary artery disease, hypertension, and hyperlipidemia. Prior medication consists of 100 mg aspirin, 5 mg bisoprolol, and 40 mg simvastatin. Initial blood glucose is 5.6 mmol/L and blood pressure is 150/90 mmHg. Computed tomography does not reveal any pathology. Intravenous recombinant tissue-plasminogen activator (rt-PA) is rapidly administered 225 minutes after symptom onset.

There is uncertainty about how to proceed with preexisting statin treatment in the acute setting of thrombolysis. Several studies linked statin treatment with an increased risk of intracerebral hemorrhage (ICH) after stroke, and additional studies recently indicated an increased risk for ICH after thrombolysis.1-4 This is in line with earlier epidemiological evidence showing an inverse correlation of cholesterol and ICH risk.5,6 Should statin treatment be discontinued following the principle “primum nil nocere” (Latin: first of all, do not harm)? On the contrary, there is strong evidence that discontinuation of statin therapy during acute vascular events, including ischemic as well as hemorrhagic stroke, impairs vascular function and dramatically decreases the chances of good outcome and survival.7-10 In this opinion article, we would like to make a strong case that preexisting statin treatment should not be paused or abruptly discontinued, either in acute ischemic stroke patients receiving rt-PA or in patients with acute ICH.

What is the evidence that stroke patients on statins have a higher risk of ICH? The evidence for risks and benefits of statins after stroke are mainly derived from the Heart Protection Study and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.1,2 A subgroup analysis of the Heart Protection Study focusing on 3280 patients with prior cerebrovascular disease found higher absolute numbers of hemorrhagic strokes in the statin group (21 vs 11), but this was not significant.1 Also, in the SPARCL trial follow-up period, more hemorrhagic strokes were observed in atorvastatin-treated than in placebo-treated patients (55 vs 33).2 The Multiple Risk Factor Intervention Trial already demonstrated in the late 1980s that there may be an inverse correlation of cholesterol levels and death from hemorrhagic strokes in men.5

In accordance, the case-control study INTERSTROKE demonstrated higher non-high-density lipoprotein (HDL) cholesterol to be associated with a lower risk of intracerebral hemorrhage.6 Consequently, several studies tested the hypothesis that prior statin use increases the frequency of ICH (hemorrhagic transformation or parenchymal hemorrhage) after intravenous thrombolysis for ischemic stroke. In fact, statins reduce thrombin generation and modify fibrinolytic balance by upregulating endogenous rt-PA production and reducing plasminogen activator-inhibitor 1 expression.11,12 This might lead not only to enhanced efficacy of rt-PA, but also to an increased risk of ICH. In a study of 311 consecutive ischemic stroke patients who underwent intraarterial thrombolysis, ICH was observed more often in statin users than in nonusers (adjusted odds ratio [OR], 3.1; 95% confidence interval [CI], 1.53–6.39). Symptomatic parenchymal hematoma type 2 was also detected more often in statin users (10.9% vs 3.5%, \( P = 0.02 \)). In addition, Bang et al suggested an independent association between low-low-density lipoprotein (LDL) cholesterol (but not statins) and ICH after thrombolysis in a cohort of 104 patients treated with intravenous rt-PA, intraarterial rt-PA, or both.13

Recently, however, these findings have been put into perspective by larger multicenter studies. The largest database was created by Engelter et al, who reported on >4000 ischemic stroke patients receiving intravenous rt-PA in 11 stroke units in several European countries. In a multivariable regression analysis, statin treatment was not associated with any ICH (OR, 1.15; 95% CI, 0.93–1.41) or symptomatic ICH (OR, 1.32; 95% CI, 0.94–1.85).14 Nor was an association of LDL cholesterol levels with risk of ICH observed in a large German thrombolysis database or in a pooled analysis of European thrombolysis registries encompassing 1847 patients.15,16

The Table provides a survey of observational studies reporting outcome or symptomatic ICH after thrombolysis in patients with prior statin use. Most previous studies described positive ORs for the association of pre–rt-PA statin use with ICH. However, although statin use might have an ICH-promoting effect, its magnitude appears to be low. Statin use might be an indicator of unfavorable patient characteristics, which increase the risk of ICH. For instance, statin users...
are older, are more often men, more often use concomitant antiplatelet drugs, and are more likely to have a medical history of stroke, diabetes mellitus, and hypertension compared with nonstatin users.14 Hence, smaller, nonrandomized studies reporting an association of statins and ICH might not have been sufficiently powered to control for all possible confounders. Moreover, previous studies used substantially differing definitions of ICH. It is important to note that not every type of ICH after thrombolysis accounts for clinical worsening or is associated with worse outcome.26,27 For instance, early reperfusion after vessel occlusion is frequently accompanied by benign hemorrhagic transformation.28 In fact, coadministration of rt-PA and statins has been associated in experimental29 and clinical studies,30,31 with improved rates of recanalization and reperfusion after vessel occlusion. There is further experimental evidence of beneficial interactions of rt-PA and statins. In rodent models of embolic middle cerebral artery occlusion, coadministration of rt-PA and atorvastatin 4 hours after middle cerebral artery occlusion was associated with increased cerebral blood flow, lower infarct volume, and better behavioral testing results. Interestingly, these findings were accompanied by improved microvessel integrity in the combination groups, as indicated by downregulation of rt-PA–aggravated genes related to secondary tissue injury and blood–brain barrier leakage.32,33 For instance, early reperfusion after vessel occlusion is frequently accompanied by benign hemorrhagic transformation.28

### Table. Survey of Observational Studies Reporting on Impact of Statin Use on Symptomatic ICH or Outcome After Thrombolysis

<table>
<thead>
<tr>
<th>Author Reference</th>
<th>Study Setting</th>
<th>Sample Size</th>
<th>Statin Users (%)</th>
<th>siICH Definition*</th>
<th>Adjusted OR for ICH (95%CI)</th>
<th>Adjusted OR for Favorable Outcome (95%CI)</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez-Sabin17 and Montaner18</td>
<td>Monocenter</td>
<td>145</td>
<td>26 (18)</td>
<td>Any clinical worsening associated with HT</td>
<td>No difference (n.r.)</td>
<td>5.26 (1.48–18.72)‡</td>
<td>Subgroup of patients with MCA occlusion treated within 3 h</td>
</tr>
<tr>
<td>Bang15</td>
<td>Monocenter</td>
<td>104</td>
<td>26 (25)</td>
<td>Any clinical worsening associated with HT</td>
<td>n.r. (n.r.)</td>
<td>n.r.</td>
<td>Mixed cohort of intravenous or intraarterial thrombolysis or embolectomy, low LDL associated with ICH</td>
</tr>
<tr>
<td>Cappellari19</td>
<td>Monocenter</td>
<td>178</td>
<td>42 (24)</td>
<td>Similar to ECASS-II</td>
<td>6.65 (1.58–29.12)</td>
<td>Unadjusted n.s., adjusted n.r.</td>
<td>Not adjusted for age, stroke severity, and several baseline characteristics.</td>
</tr>
<tr>
<td>Engelter14</td>
<td>Multicenter</td>
<td>4012</td>
<td>918 (23)</td>
<td>Any ICH</td>
<td>1.15 (0.93–1.41)</td>
<td>0.92 (0.89–1.29)‡</td>
<td></td>
</tr>
<tr>
<td>Makihara20</td>
<td>Multicenter</td>
<td>489</td>
<td>60 (12)</td>
<td>Any ICH within 36 h</td>
<td>1.20 (0.58–2.45)</td>
<td>0.95 (0.52–1.74)†</td>
<td>Higher HDL cholesterol predicts favorable outcome</td>
</tr>
<tr>
<td>Martinez-Ramirez21</td>
<td>Monocenter</td>
<td>182</td>
<td>30 (16)</td>
<td>Similar to SITS-MOST</td>
<td>1.71 (0.17–17.05)</td>
<td>0.79 (0.36–1.73)‡</td>
<td>No difference regarding PH type 2 (3% vs 5%; P=0.99)</td>
</tr>
<tr>
<td>Meier3</td>
<td>Monocenter</td>
<td>311</td>
<td>55 (18)</td>
<td>Any ICH within 24 h</td>
<td>3.1 (1.53–6.39)</td>
<td>n.r. (n.r.), P=0.73‡</td>
<td>Intraarterial thrombolysis only, siICH more likely in statin users (P=0.02)</td>
</tr>
<tr>
<td>Miedema22</td>
<td>Monocenter</td>
<td>476</td>
<td>98 (21)</td>
<td>Similar to SITS-MOST</td>
<td>1.6 (0.57–4.37)</td>
<td>1.11 (0.61–2.01)‡</td>
<td>Partly same cohort as Uyttenboogaart23</td>
</tr>
<tr>
<td>Own data24</td>
<td>Monocenter</td>
<td>481</td>
<td>83 (17)</td>
<td>ECASS-II</td>
<td>1.32 (0.46–3.79)</td>
<td>1.22 (0.68–2.20)‡</td>
<td>Statins might prevent poststroke pneumonia; data regarding siICH not reported in paper</td>
</tr>
<tr>
<td>Restrepo25</td>
<td>Monocenter</td>
<td>142</td>
<td>22 (15)</td>
<td>ECASS-II</td>
<td>1.1 (n.r.) P=0.87</td>
<td>3.22 (0.57–18.03)†</td>
<td>Mixed cohort of intravenous or intraarterial thrombolysis or embolectomy</td>
</tr>
<tr>
<td>Rocci13</td>
<td>Monocenter</td>
<td>1066</td>
<td>209 (21)</td>
<td>Any ICH</td>
<td>1.21 (0.79–1.8)</td>
<td>1.14 (0.76–1.73)‡</td>
<td>Low HDL might predict mortality</td>
</tr>
<tr>
<td>Uyttenboogaart23</td>
<td>Monocenter</td>
<td>252</td>
<td>39 (16)</td>
<td>Deterioration with compatible HT on CT</td>
<td>0.99 (0.18–5.43)</td>
<td>0.70 (0.25–1.94)‡</td>
<td>High triglycerides associated with ICH. Partly same cohort as Miedema22</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CT, computed tomography; ECASS-II, European Cooperative Acute Stroke Study II; h, hours; HT, hemorrhagic transformation; MCA, middle cerebral artery; n.r., not reported; n.s., not significant; OR, odds ratio; PH, parenchymal hematoma; siICH, symptomatic intracerebral hemorrhage; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*ECASS II criteria define siICH as a hemorrhage visible on follow-up imaging performed up to 36 h after treatment combined with clinical deterioration of ≥4 points on the NIHSS or death; SITS-MOST criteria define siICH as a local or remote parenchymal hematoma type 2 on follow-up imaging scan performed 22 to 36 h after treatment combined with clinical deterioration of ≥4 points on the NIHSS or death. For instance, early reperfusion after vessel occlusion is frequently accompanied by benign hemorrhagic transformation.28 In fact, coadministration of rt-PA and statins has been associated in experimental29 and clinical studies,30,31 with improved rates of recanalization and reperfusion after vessel occlusion. There is further experimental evidence of beneficial interactions of rt-PA and statins. In rodent models of embolic middle cerebral artery occlusion, coadministration of rt-PA and atorvastatin 4 hours after middle cerebral artery occlusion was associated with increased cerebral blood flow, lower infarct volume, and better behavioral testing results. Interestingly, these findings were accompanied by improved microvessel integrity in the combination groups, as indicated by downregulation of rt-PA–aggravated genes related to secondary tissue injury and blood–brain barrier leakage.32,33

Discontinuation of statins after acute stroke means withholding a drug that improves the chance of good functional outcome. Statins improve endothelial function, increase blood flow, exert anti-inflammatory and immunomodulatory effects, reduce coagulation and thrombosis, and show
Within the last few years, evidence has accumulated that statins used before and after ischemic stroke considerably improve functional outcomes and survival. In a US multicenter study analyzing medical records from 12,689 ischemic stroke patients, both prestroke and poststroke statin treatment were associated with significantly reduced 1-year mortality (hazard ratio, 0.85; 95% CI, 0.79–0.93 and hazard ratio, 0.55; 95% CI, 0.50–0.61, respectively). Moreover, patients who used statins before and after stroke were more likely to be discharged to home. This is supported by a meta-analysis including 12 observational studies comprising >11,000 patients. Pretreatment with statins was significantly associated with improved functional outcome (OR, 1.62; 95% CI, 1.39–1.88). In addition, our group recently detected a lower frequency of poststroke pneumonia in thrombolyzed patients with prior statin use, which might also contribute to the observed improvement of functional outcome after stroke.

However, the huge reduction of mortality observed in statin users might be attributed, in part, to the retrospective and observational design of previous studies. These studies thus carry the potential of confounding by indication bias. It is possible that statin therapy was not initiated in patients considered to have too poor a prognosis.

This reinforces the need for more randomized controlled trials. Clearer evidence for the impact of early initiation of statin treatment on outcome after ischemic stroke will hopefully emerge from the Stroke Treatment With Acute Reperfusion and Simvastatin trial, which will soon be completed. Evidence derived in the subgroup of patients receiving thrombolysis in the Stroke Treatment With Acute Reperfusion and Simvastatin trial will also contribute to clarifying the effect of early statin treatment on ICH after thrombolysis.

What is the evidence that long-term statin treatment increases the risk of primary ICH? The analyses of the Heart Protection Study and SPARCL trial linking statins to ICH were post hoc, with a relatively low number of ICH events. In a subgroup of patients in the SPARCL trial, hemorrhagic stroke was the entry event and a strong predictor of ICH during follow-up. With regard to the SPARCL trial, current guidelines of the American Heart Association conclude that there is insufficient data to recommend restrictions on the use of statins in patients with ICH. In fact, last year, interesting data emerged that helped to more accurately define the true impact of statin therapy on ICH risk. Hackam et al conducted a large retrospective population-based study, including >17,000 patients with a history of ischemic stroke who were followed for a median of 4 years. Overall, 213 ICH events were observed, almost twice as many as was observed in SPARCL and the Heart Protection Study together. Statin use was not associated with a higher risk of ICH; indeed, it even showed a slightly lower (albeit, not significantly lower) risk (hazard ratio, 0.87; 95% CI, 0.65–1.17). In an extensive meta-analysis of 23 randomized trials with a cumulative total of >500,000 patient-years, Hackam et al found no significant association of statin treatment with ICH (OR, 1.10; 95% CI, 0.86–1.42). Note of the authors also focused on studies enrolling exclusively patients with a history of cerebrovascular disease and found no evidence that statins increase bleeding risk in this subgroup of patients (risk ratio, 1.03; 95% CI, 0.82–1.30).

Contrary to the intuition of many clinicians, there is evidence that statins are beneficial in the acute setting of ICH. In experimental ICH, rats treated with statins after induction of ICH had lower perihematomal cell death, decreased hematoma volumes, and better functional testing results. Recently, Biffi et al conducted a meta-analysis comprising >2,500 ICH patients; the analysis included their own data and 6 previously published studies. Statin use before ICH was associated with favorable outcome (OR, 1.91; 95% CI, 1.38–2.65) and reduced mortality (OR, 0.55; 95% CI, 0.42–0.77) without evidence for heterogeneity or publication bias.

Taken together, available data do not indicate that statin treatment confers a substantially higher risk of ICH in patients on long-term statin treatment. The only subgroup of patients for whom continuation of statin therapy should be critically discussed is that of chronic ICH patients with low risk of ischemic stroke or myocardial infarction but high risk of ICH recurrence, for example, after primary lobar ICH. However, it is important to point out that an established statin therapy should probably not be discontinued in the setting of the acute event.

What are the consequences of statin discontinuation after acute cerebrovascular events? It has been demonstrated that abrupt discontinuation leads to a rebound effect and an overshoot reversal of many beneficial pleiotropic effects. For example, a rapid decrease of nitric oxide bioavailability below baseline levels, an increase of platelet activation, and augmented production of reactive oxygen species were observed in vitro and in animal studies after discontinuation of prior statin treatment. In fact, patients who discontinued established prior statin therapy after hospitalization for acute coronary syndrome had a higher risk of cardiac complications or out-of-hospital death. Important data for adverse effects after statin discontinuation in the setting of acute ischemic stroke were published by Blanco et al. The authors randomly assigned patients with prestroke statin use to either stop statin treatment for the first 3 days after admission or to continue statin treatment with atorvastatin. After 3 months, clinical outcome worsened in those patients who discontinued statin treatment, and they were more likely to experience early neurological deterioration. Increase of infarct volume was also significantly higher in the discontinuation group. These findings have been acknowledged by the guidelines of the European Stroke Organisation, which states that “statin withdrawal at the acute stage of stroke may be associated with an increased risk of death or dependency.” The association of discontinued statin therapy with worse clinical outcome after ischemic stroke is supported by recent analyses by Flint et al. The authors analyzed medical records from >12,000 ischemic stroke patients treated in hospitals belonging to a large US integrated healthcare delivery system. Even a brief discontinuation of statins for >2 days after acute ischemic stroke resulted in a significantly higher mortality after 1 year (46% vs 22%; hazard ratio, 2.5; 95% CI, 2.1–2.9). Similar results were found regarding the probability of patient discharge to home (OR, 0.77; 95% CI, 0.63–0.94).
Statin discontinuation also seems to be harmful to patients with hemorrhagic stroke. A Canadian multicenter study reported data on 2466 consecutive ICH patients. Patients who discontinued statins after ICH were more likely to have poor clinical outcome (OR, 2.4; 95% CI, 1.13–4.56) or to die within 30 days (OR, 2.0; 95% CI, 1.30–3.04).10

One might argue that most clinical data originate from observational studies, which are prone to confounding by indication. Hence, statins might have been continued only in those patients expected intuitively by physicians to benefit from them. For example, in the study by Dowlatshahi et al, the effect of cessation of statins was markedly attenuated after exclusion of patients treated with palliative strategy in the hospital.10 Nevertheless, even if the magnitude of statin discontinuation effect is smaller than what is indicated by observational studies, there is no evidence that its cessation within the first days after an acute cerebrovascular event would be beneficial (even in patients suffering from ICH).

Conclusions

In conclusion, we would argue strongly that prior statin treatment should not be discontinued, paused, or reduced in patients with acute ischemic stroke, and that this also includes patients undergoing thrombolysis. In addition, we recommend that in patients with primary ICH, prior statin treatment should also not be discontinued in the acute phase. Rather, a decision to continue or discontinue statin medication should be made in the chronic phase after clinical stabilization. Available experimental and clinical evidence points to a beneficial impact of statins on stroke outcome and survival, both in patients with ischemic stroke and in those with hemorrhagic stroke. Even if there truly is a higher risk of hemorrhagic complications after thrombolysis, the risk appears to be modest and has to be balanced against the beneficial neuroprotective effects of statins and the detrimental consequences of statin discontinuation shortly after a cerebrovascular event.

Acknowledgments

We thank Catherine Aibling for a critical reading of the manuscript.

Sources of Funding

The authors received funding from the German BMBF (Center for Stroke Research Berlin 01 EO 0801). Dr Endres receives funding from the DFG (Excellence cluster NeuroCure; SFB TR 43, KFO 247, KFO 213), BMBF (Centre for Stroke Research Berlin), EU (Eustroke, ARISE, WakeUp), Volkswagen Foundation (Lichtenberg Program) and Corona Foundation

Disclosures

J.S. reports travel expenses paid by Boehringer-Ingelheim. C.N. reports consulting fee/honorarium and travel/accommodations/meeting expenses paid by Boehringer-Ingelheim and Pfizer and a payment for development of educational presentations by TAKEDA. M.E. has received grant support from AstraZeneca and Sanofi, and has participated in advisory board meetings of Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Pfizer, and Sanofi, and has received honoraria from Astra Zeneca, Bayer, Berlin Chemiec, Bristol-Myers Squibb, Boehringer-Ingelheim, Desitin, Eisei, Ever, Glaxo Smith Kline, MSD, Novartis, Pfizer, Sanofi, Takeda, and Trommsdorff.

References


Should Statins Be Paused or Discontinued After Thrombolysis or Acute Intracerebral Hemorrhage? No!
Jan F. Scheitz, Christian H. Nolte and Matthias Endres

*Stroke*. 2013;44:1472-1476; originally published online February 26, 2013;
doi: 10.1161/STROKEAHA.111.000001

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/5/1472

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/