Statin use and outcome after intracerebral hemorrhage

Case-control study and meta-analysis

A. Biffi, MD
W.J. Devan, BS
C.D. Anderson, MD
A.M. Ayres, BA
K. Schwab, BA
L. Cortellini, MSc
A. Viswanathan, MD, PhD
N.S. Rost, MD
E.E. Smith, MD, MPH
J.N. Goldstein, MD, PhD
S.M. Greenberg, MD, PhD
J. Rosand, MD, MSc

Address correspondence and reprint requests to Dr. Jonathan Rosand, Center for Human Genetic Research, Massachusetts General Hospital, 185 Cambridge Street, CPZN-6818, Boston, MA 02114
jrosand@partners.org

ABSTRACT

Objectives: Intracerebral hemorrhage (ICH) is a highly lethal disease of the elderly. Use of statins is increasingly widespread among the elderly, and therefore common in patients who develop ICH. Accumulating data suggests that statins have neuroprotective effects, but their association with ICH outcome has been inconsistent. We therefore performed a meta-analysis of all available evidence, including unpublished data from our own institution, to determine whether statin exposure is protective for patients who develop ICH.

Methods: In our prospectively ascertained cohort, we compared 90-day functional outcome in 238 pre-ICH statin cases and 461 statin-free ICH cases. We then meta-analyzed results from our cohort along with previously published studies using a random effects model, for a total of 698 ICH statin cases and 1,823 non–statin-exposed subjects.

Results: Data from our center demonstrated an association between statin use before ICH and increased probability of favorable outcome (odds ratio [OR] = 2.08, 95% confidence interval [CI] 1.37–3.17) and reduced mortality (OR = 0.47, 95% CI 0.32–0.70) at 90 days. No compound-specific statin effect was identified. Meta-analysis of all published evidence confirmed the effect of statin use on good outcome (OR = 1.91, 95% CI 1.38–2.65) and mortality (OR = 0.55, 95% CI 0.42–0.72) after ICH.

Conclusion: Antecedent use of statins prior to ICH is associated with favorable outcome and reduced mortality after ICH. This phenomenon appears to be a class effect of statins. Further studies are required to clarify the biological mechanisms underlying these observations.
Neurology® 2011;76:1581–1588

GLOSSARY

CI = confidence interval; **GCS** = Glasgow Coma Scale score; **ICH** = intracerebral hemorrhage; **LDL** = low-density lipoprotein; **MGH** = Massachusetts General Hospital; **mRS** = modified Rankin Scale; **OR** = odds ratio.

Intracerebral hemorrhage (ICH) accounts for 15% of all acute strokes, with societal and public health ramifications largely determined by the associated prognosis.[1] Despite substantial advances in the field of neurocritical care, more than half of patients with ICH face the prospect of death or severe disability.[2] New research directions are therefore crucially needed in order to understand the complex pathophysiology of ICH outcome and recovery and exploit this understanding to benefit patients.[3]

Several studies investigating animal models of ICH suggest that statins exert a beneficial effect on functional recovery.[4–6] These findings could be explained by the effect of statins on lipid metabolism, or by other effects including neuroprotection and stimulation of neurogenesis and synaptogenesis.[7,8] Evidence from observational studies in patients, however, is conflicting, with some groups

Supplemental data at www.neurology.org

e-Pub ahead of print on March 30, 2011, at www.neurology.org.

From the Hemorrhagic Stroke Research Group (A.B., W.J.D., C.D.A., A.M.A., K.S., L.C., A.V., N.S.R., J.N.G., S.M.G., J.R.), Division of Neurocritical Care and Emergency Neurology, Department of Neurology (A.B., W.J.D., C.D.A., L.C., N.S.R., J.N.G., J.R.), Center for Human Genetic Research (A.B., W.J.D., C.D.A., L.C., N.S.R.), and Department of Emergency Medicine (J.N.G.), Massachusetts General Hospital, Boston; and Department of Clinical Neurosciences (E.E.S.), University of Calgary, Calgary, Canada.

Study funding: Supported by the Deane Institute for Integrative Study of Atrial Fibrillation and Stroke, the NIH/NINDS, and the American Heart Association/Bugher Foundation Centers for Stroke Prevention Research. The funding entities had no involvement in study design, data collection, analysis, or interpretation, writing of the report, or in the decision to submit the paper for publication.

Disclosure: Author disclosures are provided at the end of the article.

Table 1 MGH cohort characteristics[a]

Variable	Statin	Statin-free	*p* Value
No. of subjects	238	461	
Age, y, mean (SD)	74.2 (9.6)	72.0 (12.8)	0.004[b]
Gender	100 (0.42)	221 (0.48)	0.14
Caucasian	214 (0.90)	406 (0.88)	0.27
Education, y			0.42
1–6	5 (0.02)	9 (0.02)	
7–9	14 (0.06)	32 (0.07)	
10–13	109 (0.46)	208 (0.45)	
≥14	110 (0.46)	212 (0.46)	
Hypertension	209 (0.88)	350 (0.76)	<0.001[b]
Type 2 diabetes	76 (0.32)	92 (0.20)	<0.001[b]
Coronary artery disease	100 (0.42)	69 (0.15)	<0.001[b]
Atrial fibrillation	71 (0.30)	83 (0.18)	<0.001[b]
Previous history of dementia	38 (0.16)	65 (0.14)	0.44
Previous ischemic stroke/TIA	48 (0.20)	69 (0.15)	0.08
Previous history of ICH	17 (0.07)	28 (0.06)	0.58
Pre-ICH mRS >2	27 (0.11)	60 (0.13)	0.31
Antihypertensive agent use	140 (0.59)	228 (0.50)	0.02[b]
Glycemic control agent use	58 (0.76)	73 (0.79)	0.005[b]
Warfarin use	90 (0.38)	88 (0.19)	<0.001[b]
Antiplatelet agent use	143 (0.60)	184 (0.40)	<0.001[b]
Glasgow Coma Scale score at admission			0.69
3–10	36 (0.15)	83 (0.18)	
11–14	48 (0.20)	97 (0.21)	
15	154 (0.65)	281 (0.61)	
ICH location			0.83
Lobar	103 (0.43)	189 (0.41)	
Deep	108 (0.45)	217 (0.47)	
Cerebellar	19 (0.08)	37 (0.08)	
Multiple locations	7 (0.03)	14 (0.03)	
Primary IVH	1 (0.004)	4 (0.01)	
Baseline ICH volume, cc			
Median (interquartile range)	17.9 (5.7–45.5)	19.0 (6.0–49.0)	0.78
<30	129 (0.54)	254 (0.55)	0.78
30–60	45 (0.19)	92 (0.20)	
>60	64 (0.27)	115 (0.25)	
Intraventricular extension	119 (0.50)	254 (0.55)	0.20
Hematoma expansion[c,d]	24 (0.14)	44 (0.14)	0.89
Patient admission			0.16
Presented directly to study center	76 (0.32)	166 (0.36)	
Transferred from outside hospital	162 (0.68)	295 (0.64)	
Time from symptom onset to admission, median (interquartile range in hours)	5.4 (1.1–14.3)	5.9 (1.0–13.8)	0.51
Time from symptom onset to baseline imaging, median (interquartile range in hours)	6.9 (1.8–17.4)	7.4 (1.5–18.6)	0.42
Time between baseline and follow-up imaging,[d] median (interquartile range in hours)	17.5 (8.2–28.3)	18.1 (9.0–27.6)	0.58

—Continued

reporting reduced mortality or improved outcome after ICH in individuals using statins before the event, and others failing to replicate this association.[9–14]

We performed a meta-analysis of all available evidence to clarify whether pre-ICH statin use influences functional outcome and mortality. In order to increase our statistical power, we included new unpublished data from our group at Massachusetts General Hospital (MGH) and added these results to the meta-analyses. We also investigated whether any effect of statins could be explained by their impact on known neuroimaging predictors of ICH outcome (admission ICH volume, presence of hematoma expansion, and presence of intraventricular extension).[15–17] Finally, we sought to determine whether specific statin compounds showed differential effects on outcome.

METHODS

MGH cohort. ***Patient recruitment and follow-up.*** Subjects were drawn from an ongoing longitudinal cohort study of primary ICH as previously described.[13] Briefly, study subjects were consecutive patients age ≥18 years admitted to the MGH Emergency Department from September 1, 2005, to December 31, 2009, with primary ICH. These enrollment criteria ensured that no overlap in recruited subjects was present with a previously published report from our group.[13] All patients with a baseline admission CT scan and determination of functional status at 90 days were eligible. For the present study, follow-up CT scans within 48 hours of admission were also analyzed where available.

Clinical data were recorded at the time of index presentation by stroke neurologists and full-time study personnel as part of routine clinical care. Collected data included information on demographics, previous medical history, Glasgow Coma Scale score (GCS), and pre-ICH medication use (including statin use). Specifically, subjects were confirmed to be on statin therapy for at least 1 month prior to admission. All admission and follow-up CT scans were reviewed by study investigators blinded to clinical and drug exposure data, to confirm ICH location and identify signs of intraventricular extension. ICH volume (both at admission and follow-up) was calculated as previously described.[16] Serum total cholesterol and low-density lipoprotein (LDL) cholesterol levels obtained from clinical blood draws performed within 48 hours of ICH symptom onset were extracted via review of electronic medical records where available. Additionally, we collected first available total and LDL cholesterol data (regardless of time of blood draw) for all included subjects for sensitivity analyses purposes.

Patients and their caregivers were interviewed by telephone at 3 months post-ICH to assess functional outcome using the modified Rankin Scale (mRS) score.[13] The use or discontinuation of medications after discharge was specifically assessed in this interview.

Standard protocol approvals, registrations, and patient consents. This study was performed with approval of the MGH

Table 1 Continued

Variable	Statin	Statin-free	p Value
DNR or CMO orders	74 (0.31)	152 (0.33)	0.34
Intubation required	90 (0.38)	184 (0.40)	0.32
ICP monitor placed	12 (0.05)	18 (0.04)	0.30
EVD placed	35 (0.15)	78 (0.17)	0.26
Surgical hematoma evacuation	21 (0.09)	37 (0.08)	0.41
Duration of hospital stay, d			0.73
1–3	52 (0.22)	106 (0.23)	
3–5	60 (0.25)	111 (0.24)	
6–10	78 (0.33)	157 (0.34)	
≥11	48 (0.20)	87 (0.19)	
Admission systolic blood pressure, mm Hg	181 (2.2)	178 (2.1)	0.35
Admission diastolic blood pressure, mm Hg	95 (1.5)	94 (1.9)	0.69
Total cholesterol, mg/dL, mean (SD)[e]	179 (35)	191 (42)	0.004[b]
LDL cholesterol, mg/dL, mean (SD)[e]	97 (28)	108 (34)	<0.001[b]
90-day favorable outcome (mRS 0–2)	60 (0.25)	87 (0.19)	0.03[b]
90-day mortality	109 (0.46)	267 (0.58)	0.002[b]

Abbreviations: CMO = comfort measures only; DNR = do not resuscitate; EVD = extraventricular drain; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IVH = intraventricular hemorrhage; LDL = low-density lipoprotein; MGH = Massachusetts General Hospital; mRS = modified Rankin Scale.

[a] All variables reported as number (% of total) unless otherwise specified.

[b] Significant.

[c] Defined as >33% increase in ICH volume comparing follow-up and admission CT scan.

[d] Follow-up CT scans were available for 543 subjects (78% of cohort).

[e] Cholesterol data available for 520 subjects (74% of cohort).

institutional Review Board and all subjects or their guardians provided written informed consent prior to participation.

Outcomes and definitions. Consistent with prior studies, favorable functional outcome was defined as a 90-day mRS ranging from 0 to 2.[9–14] Sensitivity analyses using a definition of mRS ranging from 0 to 3 returned very similar results (data not shown). Pre-ICH statin use was analyzed as a binary variable. We also separately recorded the specific compound prescribed and analyzed each one separately. Additional analyses were performed adjusting for statin dosage, defined as either high (≥50% of maximum recommended dose) or low (<50% of maximum recommended dosage).[13] Age at index ICH was analyzed as a continuous variable. GCS was categorized to the following cutpoints: 15, 11–14, and 3–10. ICH volume was analyzed as both a continuous variable (after log-transformation to achieve normality) and according to the following cutoffs: <30 mL, 30–60 mL, >60 mL. Hematoma expansion was defined as a binary outcome, based on a cutoff of at least 33% increase in ICH volume comparing follow-up and admission CT scans. Intraventricular extension was also defined as a binary outcome based on qualitative assessment of admission scans. Total cholesterol and LDL cholesterol admission values were analyzed as continuous variables.

Statistical methods. Categorical variables were compared using Fisher exact test and continuous variables using the Mann-Whitney rank-sum or unpaired *t* test as appropriate. To determine the influence of pre-ICH statin use on functional outcome, mortality, hematoma expansion, and intraventricular extension, we used logistic regression analyses. Potential associations between statin use and ICH volume were analyzed using linear regression. Candidate covariates included all variables showing a trend in association with outcome or mortality in univariate analysis ($p < 0.20$), as well as variables showing trends toward differential distribution in statin users vs nonusers ($p < 0.20$). Backward elimination of nonsignificant variables ($p > 0.05$) was subsequently used to generate a minimal model. We separately analyzed effects of different statins on outcome and mortality, and compared them using the Breslow-Day test. Significance threshold was set at $p < 0.05$ (2-tailed) for all analyses. All analyses were performed with the *R* software v2.10.0. All significance tests were 2-tailed with significance threshold set at $\alpha = 0.05$. Power calculations were performed using the pwr.f2.test function in the pwr library for *R* v2.10.0, assuming statistical power = 0.80 and $\alpha = 0.05$.

Meta-analysis. ***Literature search and study inclusion criteria.*** A literature search was performed independently by A.B. and W.J.D. in order to identify human studies in English language exploring the effect of statin use on functional outcome, mortality, or both after ICH. Search terms and workflow used are shown in figure e-1 on the *Neurology*® Web site at www.neurology.org. Queried databases included PubMed, Medline, Embase, and Ovid. Manual review of references in articles matching searching criteria was conducted to identify potential additional reports. For studies that overlapped with published reports, only the most recent comprehensive results were included in the meta-analysis. Data were retrieved and meta-analyzed independently by A.B. and W.J.D., and results compared for consistency. Where available, data for functional outcome and mortality were extracted separately and meta-analyzed accordingly.

Statistical methods. Results from multivariate regression analyses in individual studies were meta-analyzed using a conservative inverse variance-based random effects pooling method (DerSimonian-Laird).[18] Cochran Q test was used to estimate heterogeneity, followed by calculation of I^2 (percentage of effect size attributable to heterogeneity). Effect size heterogeneity was considered significant for heterogeneity *p* values <0.10 or I^2 >0.20.[19] Publication bias was quantified by inspection of funnel plots and computation of Egger and Begg tests *p* values.[19] All meta-analyses were performed using the meta library for *R* v2.10.0.

RESULTS

MGH cohort. ***Statin use and ICH outcome.*** During the enrollment period, 732 individuals presented to our center with primary ICH. Of these, 33 refused consent or did not have an admission CT scan of high enough quality for analysis. A total of 699 subjects were therefore eligible for analysis, including 238 pre-ICH statin cases and 461 statin-free cases (table 1).

For 520 subjects (74%), total and LDL cholesterol had been determined within 48 hours as part of clinical laboratory testing. These subjects did not differ from the rest of the cohort in terms of baseline characteristics presented in table 1 (all *p* values >0.20). Additionally, 543 subjects (78%) had a follow-up CT scan available for determination of hematoma expansion. These subjects did not differ from the rest of the cohort in terms of pre-ICH characteristics, including statin use ($p = 0.47$). However, they had higher baseline ICH volume,

Table 2 Univariate and multivariate analysis: Pre-ICH statin use and good functional outcome (mRS 0–2) at 90 days

	Univariate			Multivariate		
Variable	OR	95% CI	p Value	OR	95% CI	p Value
Age	0.96	0.95–0.97	<0.001	0.96	0.95–0.98	<0.001[a]
Hypertension	0.76	0.53–1.10	0.15	0.53	0.31–0.91	0.021[a]
Type 2 diabetes	0.72	0.48–1.09	0.12	—	—	>0.2
Coronary artery disease	0.32	0.20–0.53	<0.001[a]	0.32	0.16–0.65	0.001[a]
Previous dementia	0.09	0.03–0.25	<0.001[a]	0.03	0.01–0.13	<0.001[a]
Pre-ICH mRS >2	0.04	0.01–0.17	<0.001[a]	—	—	>0.2
Previous ischemic stroke/TIA	0.31	0.17–0.58	<0.001[a]	—	—	>0.2
ICH location: deep	0.73	0.52–1.02	0.061	—	—	>0.2
GCS: 15	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
GCS: 11–14	0.50	0.33–0.76	0.001[a]	0.54	0.29–1.00	0.05[a]
GCS: 3–10	0.07	0.03–0.20	<0.001[a]	0.25	0.08–0.73	0.012[a]
ICH volume: 0–30 cc	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
ICH volume: 30–60 cc	0.30	0.19–0.48	<0.001[a]	0.26	0.15–0.46	<0.001[a]
ICH volume: >60 cc	0.07	0.03–0.13	<0.001[a]	0.05	0.02–0.14	<0.001[a]
Intraventricular extension	0.18	0.12–0.25	<0.001[a]	0.40	0.24–0.68	0.001[a]
Warfarin use	0.45	0.29–0.70	<0.001[a]	0.44	0.29–0.68	0.001[a]
Statin use	1.45	1.01–2.10	0.03[a]	2.08	1.37–3.17	0.004[a]

Abbreviations: CI = confidence interval; GCS = Glasgow Coma Scale score; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; OR = odds ratio.
[a] Significant.

lower GCS score, and more frequent intraventricular extension (all p values <0.05).

Compared to statin-free individuals, ICH cases exposed to statins before the index event were older, more likely to have several comorbidities, and therefore more likely to receive several forms of drug treatment. However, treatment rates for hypertension, diabetes, and atrial fibrillation did not differ between groups ($p > 0.20$). Baseline data on the acute ICH itself and the index hospitalization did not differ between groups. Both 90-day favorable outcome (mRS 0–2) and survival were more likely in statin users in univariate analysis ($p < 0.05$).

In multivariate analysis, individuals taking statins at the time of ICH had improved functional outcome (table 2) and reduced mortality (table 3). Adjustment for statin dose did not alter results for either functional outcome (odds ratio [OR] = 2.06, $p = 0.005$) or mortality (OR = 0.45, $p = 0.001$). To eliminate, as best as possible, the unmeasured effects of withdrawal of care from our analysis, we created a separate multivariate model for favorable functional outcome including only ICH survivors at 90 days.[20,21] Pre-ICH statin use was associated with better outcome in this subset analysis (OR = 1.90, 95% confidence interval [CI] 1.15–3.15, $p = 0.012$).

Subset analyses. In order to clarify whether associations between statin use and ICH outcome could be confounded by lipid levels, we performed additional analyses adjusting for total and LDL cholesterol levels in the 520 patients with laboratory values within 48 hours available. Results from these subset analyses were in line with previously presented findings for both favorable outcome (OR = 2.07, 95% CI 1.35–3.18, $p = 0.008$) and mortality (OR = 0.47, 95% CI 0.34–0.68, $p = 0.001$). Inclusion of total and LDL cholesterol levels for all subjects (regardless of time of blood draw) also did not alter results (data not shown).

Additional analyses were performed to identify interactions between cholesterol levels and statin use, but none of the interaction terms achieved statistical significance ($p > 0.20$). Similarly, no differences in effect size for statin use were identified in multivariate models stratified by quartiles of total or LDL cholesterol levels ($p > 0.20$).

We also analyzed the subset of ICH cases with available follow-up CT scans, but adjustment for hematoma expansion or follow-up ICH volume did not alter results for either functional outcome or mortality (data not shown).

We repeated all our analyses after removing the following individuals: 1) subjects who had statins discontinued before discharge (n = 29), 2) subjects who had statins discontinued after discharge but

Table 3 Univariate and multivariate analysis: Pre-ICH statin use and 90-day mortality following ICH

	Univariate			Multivariate		
Variable	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Age	1.04	1.03–1.05	<0.001	1.05	1.03–1.06	<0.001
Type 2 diabetes	1.40	1.01–1.93	0.043	2.11	1.28–3.47	0.003
Coronary artery disease	1.76	1.28–2.41	0.001	—	—	>0.2
Pre-ICH mRS >2	1.54	0.93–2.57	0.093	—	—	>0.2
Previous dementia	1.67	1.15–2.43	0.007[a]	2.44	1.39–4.31	0.002[a]
Previous ischemic stroke/TIA	1.36	0.94–1.96	0.11	—	—	>0.2
Previous ICH	1.48	0.83–2.63	0.19	2.28	1.06–4.89	0.032[a]
GCS: 15	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
GCS: 11–14	1.83	1.23–2.71	0.003[a]	1.68	1.13–2.50	0.007[a]
GCS: 3–10	7.15	4.30–11.90	<0.001[a]	3.44	1.84–6.46	<0.001[a]
ICH volume: 0–30 cc	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
ICH volume: 30–60 cc	3.60	2.51–5.17	<0.001[a]	4.22	2.70–6.58	<0.001[a]
ICH volume: >60 cc	16.51	11.04–24.67	<0.001[a]	13.80	8.13–23.3	<0.001[a]
Intraventricular extension	5.95	4.42–8.02	<0.001[a]	3.27	2.20–4.89	<0.001[a]
Warfarin use	2.27	1.66–3.12	<0.001[a]	2.55	1.33–4.89	0.005[a]
Statin use	0.67	0.51–0.89	0.006[a]	0.47	0.32–0.70	0.005[a]

Abbreviations: CI = confidence interval; GCS = Glasgow Coma Scale score; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; OR = odds ratio.
[a] Significant.

within 90 days of the index ICH (n = 15), and 3) both previously mentioned groups (n = 44). We observed no change in results in all 3 sensitivity analyses (data not shown). Removal of statin nonusers who were started on statin therapy after discharge (n = 19) also did not alter results (data not shown).

Specific statin compounds. We analyzed different statin compounds for independent associations with outcome and mortality after ICH. Tested statins included simvastatin (n = 93) and atorvastatin (n = 102), while other compounds (pravastatin and lovastatin) were jointly analyzed due to limited sample size (n = 43). We found associations with favorable outcome and mortality for atorvastatin and simvastatin ($p < 0.05$), but no differences among agents were identified (heterogeneity of effects p value = 0.35). Furthermore, introduction of compound specification in our multivariate models as a categorical covariate did not alter results presented in tables 2 and 3, thus supporting the lack of statin-specific differential effects.

We repeated all analyses adjusting for statin dose, but failed to observe any difference in results for either specific compounds or for the heterogeneity of effects test (data not shown). Based on available sample size, our cohort had statistical power of 0.80 to detect a 20% difference in effect size for both simvastatin and atorvastatin compared to all other compounds.

Statin use and neuroimaging predictors of ICH outcome. We subsequently investigated whether the observed effect of statins could be explained by their influence on known determinants of outcome and mortality after ICH, including admission ICH volume, presence of intraventricular extension, and presence of hematoma expansion (defined as >33% increase in ICH volume comparing follow-up and admission scans). Based on available sample size, our cohort had statistical power of 0.80 to detect a statin-associated 5 mL decrease in admission ICH volume, OR of 0.70 for intraventricular extension, and an OR of 0.60 for hematoma expansion. None of these analyses identified any significant associations with pre-ICH statin use ($p > 0.20$). In order to improve our power, we pooled imaging data from subjects enrolled in the previous study from our group,[13] for a total of 387 statin users and 941 nonusers (follow-up imaging available for 252 statin users and 658 nonusers). No association with pre-ICH statin use was identified. The combined dataset had power of 0.80 to detect a statin-associated 2 mL decrease in ICH volume, OR of 0.90 for intraventricular extension, and an OR of 0.80 for hematoma expansion.

Meta-analysis. We performed 2 separate meta-analyses of the effects of statin use before ICH on favorable outcome and mortality. Our initial literature search identified 19 studies and a total of 6 studies qualified for inclusion (table 4).[9–14] These 5 studies were meta-analyzed along with new results presented above.

For favorable outcome, our meta-analysis identified an association with pre-ICH statin use: OR = 1.91, 95% CI 1.38–2.65, $p < 0.0001$. We did not

Table 4 Published studies included in meta-analysis

Study (reference)	Country	Study design	Enrollment period	Statin users	Statin nonusers	Statin dose data available	Cholesterol levels available	Outcome endpoint	Mortality endpoint, d
9	Israel	Observational	2002–2008	101	298	No	No	mRS: 0–2	90
10	Spain	Observational	1998–2007	34	235	No	Yes	mRS: 0–2	90
11	USA	Observational	1999–2006	32	93	No	Yes	mRS: 0–3	90
12	Israel multicenter	Observational	2003, 2007	89	223	No	No	mRS: 0–3	Discharge
13	USA	Observational	1998–2005	149	480	Yes	Yes	GOS: 4–5	90
14	International multicenter	Randomized clinical trial	1998–2001	55	33	Yes	Yes	mRS: 0–3	90
Present study	USA	Observational	2005–2009	238	461	Yes	Yes	mRS: 0–2	90
Meta-analysis total	—	Meta-analysis	—	698	1,823	—	—	—	—

Abbreviations: mRS = modified Rankin Scale; GOS = Glasgow Outcome Scale.

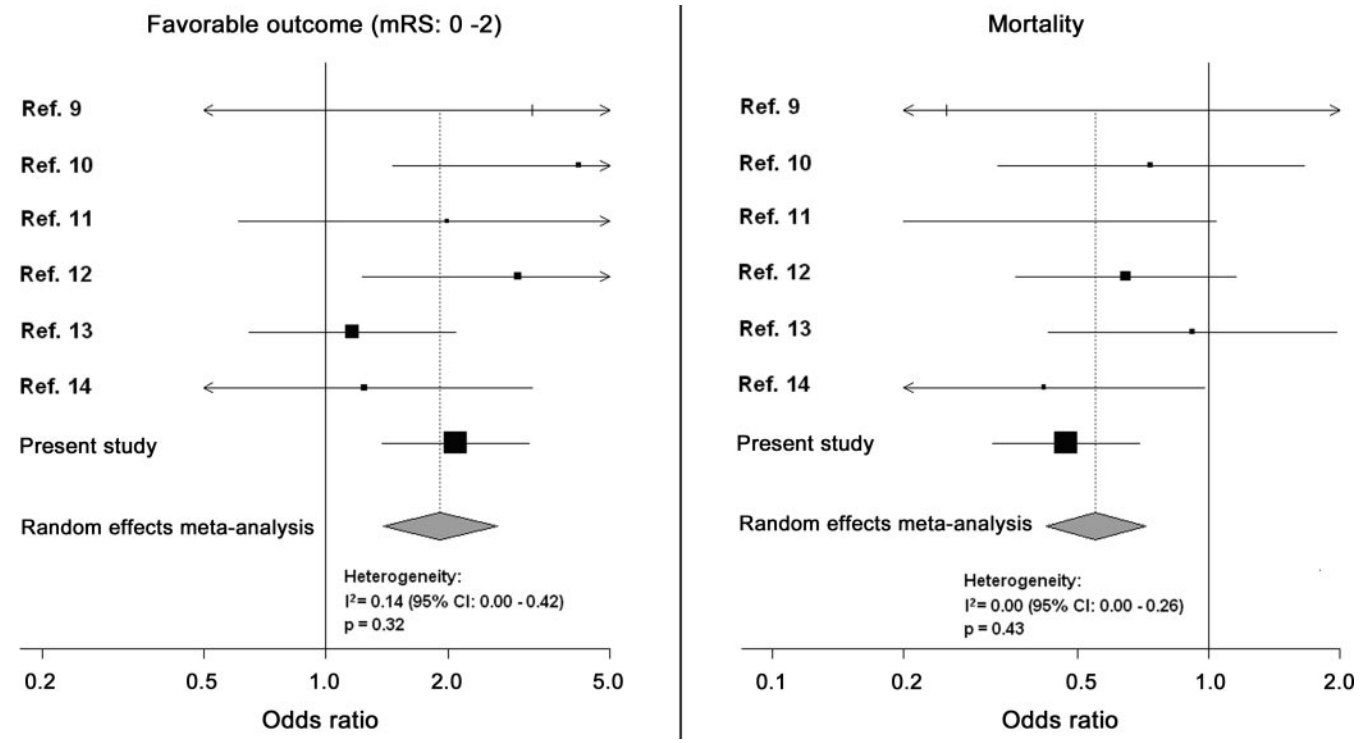
identify significant between-study heterogeneity of effect sizes (figure 1). When we meta-analyzed results for survival after ICH, we identified an association between statin use and reduced mortality: OR = 0.55, 95% CI 0.42–0.72, $p < 0.0001$, without evidence of significant heterogeneity (figure 1).

Sensitivity analyses involving sequential removal of each individual study in turn yielded very similar results for both favorable outcome and mortality endpoints. Estimation of publication bias via the Egger test and the Begg test returned nonsignificant results for both meta-analyses (all $p > 0.20$).

DISCUSSION Results from our analyses demonstrate an association between pre-ICH statin use and reduced mortality and disability at 90 days. These findings suggest a role for statins in the complex pathophysiology of ICH recovery, independent of any effect on ICH volume, the most potent ICH outcome predictor.

Prior results from our group suggested no link between statin use and outcome after ICH.[13] In contrast, new findings from data presented above point to a significant association. Several factors likely account for this discrepancy. First, the larger sample

Figure 1 Forest plots: Meta-analysis of effect of statin use on ICH outcome and mortality at 90 days



CI = confidence interval; I^2 = percent of meta-analysis effect size attributable to between study heterogeneity; mRS = modified Rankin Scale.

size (particularly in terms of number of enrolled ICH statin users) and resultant improved statistical power of the present cohort could result in a positive finding compared to previously published data. Second, our new results derive from a cohort recruited from 2005 to 2009, compared to previously published results for individuals enrolled from 1998 to 2005. Indications for statins have increased in recent years, and use of these agents has therefore become increasingly frequent.[22] This evolution in statin prescription practice may well have led to a reduction in the average comorbidity burden (compared to our previous report) among individuals receiving statins, a phenomenon that may have limited the impact of indication bias in our present analyses. Overall, published studies included in our meta-analysis, while often underpowered (due to sample size limitations or cohort characteristics as previously discussed), all point to an association between pre-ICH statin use and favorable outcome.

We separately analyzed different statin compounds to investigate whether the effect on outcome after ICH was statin-specific. While only 2 among tested statins achieved statistical significance, limited sample size appears to be the most likely explanation. Based on this analysis we cannot entirely rule out subtle differences in effect size for specific statin compounds, but our results suggest that the variation may not be clinically relevant.

Our analysis has limitations. First, the vast majority of results presented in meta-analysis are derived from observational studies, all accompanied by established limitations of this study design. These limitations include recall bias during patient follow-up and possible confounding due to propensity to receive statin treatment, particularly because of differences in socioeconomic status and health care quality/availability. We identified no differences in education, treatment rates for other chronic conditions (hypertension, diabetes), and in-hospital procedures between statin users and nonusers, but possible residual confounding cannot be ruled out entirely. However, results from one clinical trial were concordant with observational studies. Second, we meta-analyzed studies that employed different endpoints for functional outcome and mortality. However, we did not identify any significant heterogeneity across studies, and sensitivity analyses using different outcome definitions yielded very similar results. Third, cohorts participating in meta-analysis are largely composed of European ancestry individuals, thus limiting generalizability of our findings to other ethnicities at high risk for ICH.

The existence of a relationship between pre-ICH statin use and improved outcome after ICH contrasts with previous findings associating low LDL cholesterol levels at admission and ICH-related mortality.[23] Furthermore, available evidence from clinical trials suggests a link between statin use and increased risk of recurrent ICH.[24] While the lipid-lowering effect of statins could explain their detrimental long-term effect on ICH risk, we did not identify interactions between cholesterol levels and short-term benefit on functional outcome. Available evidence therefore raises the possibility that other known biological effects of statins underlie our findings. Pleiotropic mechanisms (including neuroprotection, neurogenesis, angiogenesis, regulation of peri-hematomal blood flow, and reduction of peri-hematomal edema) might be responsible for the positive influence of statins on ICH outcome.[25–30] Therefore, it appears that different phenomena may be responsible for the short- and long-term effects of statins on ICH biology.[24]

Further studies are needed to fully understand the beneficial and detrimental effects of statins in patients with ICH. While more evidence from randomized clinical trials is clearly required before statins can be assigned a role in ICH management (if any), our results suggest that additional investigation of the pleiotropic effects of statins could identify pathways for the development of novel candidate treatment for this devastating disease.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Alessandro Biffi and W.J. Devan.

ACKNOWLEDGMENT

The authors thank all clinical coordinators and research staff in the Hemorrhagic Stroke Research Group, Department of Neurology, Massachusetts General Hospital.

DISCLOSURE

Dr. Biffi receives research support from the American Heart Association/Bugher Foundation. W.J. Devan reports no disclosures. Dr. Anderson has received research support from the American Heart Association/Bugher Foundation. A.M. Ayres reports no disclosures. K. Schwab receives research support from the NIH (NINDS, NIA). L. Cortellini reports no disclosures. Dr. Viswanathan has served as consultant for Athena Diagnostics, Inc. and receives research support from the NIH/NIA. Dr. Rost serves as an Associate Editor for *Frontiers in Hospitalist Neurology* and an Assistant Editor for *Stroke* and has received research support from the NIH/NINDS, the National Stroke Association, and the American Stroke Association/Bugher Foundation. Dr. Smith serves as an Assistant Editor for *Stroke*; has received speaker honoraria from the Canadian Consortium on Dementia; serves on speakers' bureaus for QuantiaMD and BMJ Best Practice; and receives research support from the NIH, the CIHR, the Canadian Stroke Network, Alberta Innovates–Health Solutions (funded by the Alberta Heritage Fund for Medical Research), Hotchkiss Brain Institute, and the Heart and Stroke Foundation of Canada. Dr. Goldstein serves on a scientific advisory board for and received funding for travel and consulting honoraria from CSL Behring; serves on the editorial board of the *International Journal of Emergency Medicine*; and receives research support from CSL Behring and the NIH/NINDS. Dr. Greenberg serves on a data safety monitoring board for the NIH/NINDS; has received speaker honoraria from Esteve, Medtronics, Inc., and Pfizer Inc; serves on the editorial boards of *Neurology®*, *Stroke*, *Cerebrovascular Disease*, and the *Journal of Alzheimer's Disease and Other Dementias*; has served as a consultant for Roche, Janssen Alzheimer Immunotherapy, and Bristol-Myers Squibb; and

has received/receives research support from the NIH and the Alzheimer's Association. Dr. Rosand receives research support from the NIH (NINDS, NHLBI), the American Heart Association/ Bugher Foundation, and the MGH Deane Institute for Integrative Research in Atrial Fibrillation and Stroke.

APPENDIX

PubMed search terms: Intracerebral hemorrhage, Hemorrhagic stroke, ICH, Statins, Statin, Statin use, HMG-CoA reductase inhibitors, Lipids, Hyperlipidemia, LDL, Outcome, Functional outcome, Disability, mRS, Modified Rankin Score, GOS, Glasgow Outcome Scale, Mortality, Simvastatin, Atorvastatin, Lovastatin, Rosuvastatin, Pravastatin. All possible combinations of listed search terms were used and results compared.

Received November 2, 2010. Accepted in final form January 19, 2011.

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