Impact of Hyperlipidemia and Statins on Ischemic Stroke Outcomes after Intra-Arterial Fibrinolysis and Percutaneous Mechanical Embolectomy

Lucas Restrepo^a Oh Young Bang^d Bruce Ovbiagele^a Latisha Ali^a
Doojin Kim^a David S. Liebeskind^a Sidney Starkman^{a,b} Fernando Vinuela^c
Gary R. Duckwiler^c Reza Jahan^c Jeffrey L. Saver^a

Departments of ^aNeurology, ^bEmergency Medicine and ^cRadiology, David Geffen School of Medicine, University of California, Los Angeles, Calif., USA; ^dDepartment of Neurology, Samsung Medical Center, Sungkyunkwan University, Seoul, Korea

Key Words

Ischemic stroke • Thrombolysis • Percutaneous embolectomy • Statins • Hyperlipidemia

Abstract

Background: Endovascular recanalization therapies are an increasingly employed treatment strategy in acute cerebral ischemia. The determinants of the final clinical outcome after endovascular treatment have been understudied. We investigated the effects of hyperlipidemia and statins on acute ischemic stroke outcomes after endovascular procedures.

Methods: An inquiry of a prospectively maintained stroke registry was conducted. Endovascular procedures were performed using recombinant tissue plasminogen activator, prourokinase or the Merci device within 12 hours after symptom onset. The analyzed outcomes were revascularization, hemorrhage and excellent functional outcome (Rankin score of 0–1 at 3 months). The analyses included χ^2 and Wilcoxon rank sum, logistic regression (for multivariate analyses with binary outcomes) and linear regression (for continuous outcomes). Significance was set at $p < 0.05$. **Results:** We included 142 patients, 80% treated with intra-arterial fibrinolysis, 22% with percutaneous mechanical embolectomy and 27% treated with intravenous fibrinolysis prior to endovascular inter-

vention. Age (OR = 0.956, 95% CI = 0.927–0.986, $p = 0.0041$), National Institutes of Health Stroke Scale (NIHSS) score on admission (OR = 0.881, 95% CI = 0.812–0.957, $p = 0.0025$) and history of hyperlipidemia (OR = 0.284, 95% CI = 0.08–0.99, $p = 0.0478$) were negatively associated with excellent functional outcome at 3 months. Every 50 mg/dl increment in the total cholesterol level resulted in 64% decrease in the odds of excellent functional outcome (OR = 0.36, 95% CI = 0.447–0.882, $p = 0.0253$). History of hyperlipidemia decreased the likelihood of neurological improvement ($p = 0.0462$) and was associated with a higher NIHSS score at 7 days or discharge. Statin use was related to an average 6.5-unit NIHSS decrease at discharge ($p = 0.0168$). Statins were not associated with increased frequency of recanalization or symptomatic intracerebral hemorrhage. **Conclusions:** History of hyperlipidemia may have a negative impact on the outcomes of acute ischemic stroke treated with intra-arterial fibrinolysis or percutaneous mechanical embolectomy. Statin use before and after these procedures may be related to better neurological outcomes. Larger prospective studies are needed to endorse these findings.

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This paper is dedicated to the memory of Carlos J. Abad, MD – ‘whom the gods love dies young’ (Plautus).

Background

The objective of acute ischemic stroke (AIS) treatment during the initial hours after symptom onset is reperfusion of threatened cerebral tissue. Although intravenous fibrinolysis (IVF) attains this objective in about a third of the cases [1, 2] resulting in greater odds of complete neurological recovery compared to placebo, its use is limited by a narrow therapeutic window of 3–4.5 h [3–5]. Intra-arterial fibrinolysis (IAF) and percutaneous mechanical embolectomy (PME) have emerged as therapeutic options when IVF has failed to yield recanalization, or when patients do not qualify for intravenous recombinant tissue plasminogen activator (rt-PA) [5–9]. Many studies, including a controlled, randomized trial, show that IAF improves the functional and neurological outcomes if performed during the initial hours after symptom onset [5–7]. However, recanalization cannot be achieved in about half of the IAF and PME cases [6–10] and the risk of symptomatic intracerebral hemorrhage (ICH) is greater with endovascular procedures than IVF [5, 6]. Lastly, to the dismay of treating physicians, excellent angiographic results may not correlate with satisfactory clinical improvement. Thus, there is a pressing need to know if any modifiable factors are associated with poor outcomes after endovascular procedures, in order to target them aggressively.

The interest in the effect of hyperlipidemia on AIS outcome was rekindled by the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, in which treatment with atorvastatin was associated with a relative reduction of 16% in the risk of recurrent stroke compared to placebo [11, 12]. Although the beneficial events of statins transcend mere lipid-lowering, it remains unclear whether total cholesterol and low-density lipoprotein (LDL) reduction is a desirable objective after AIS as it is for coronary artery disease (CAD) [13, 14]. Gemfibrozil, an unrelated lipid-lowering agent, can also reduce ischemic stroke risk, transient ischemic attack and need for carotid endarterectomy in CAD patients [15]. As statin use for primary and secondary stroke prevention increases, fewer patients will have AIS, but a greater proportion of cases experiencing incident events will be on statins. Accordingly, there is a need to understand the impact of baseline lipid profiles and statin therapy on AIS outcomes. Moreover, as early initiation of secondary prevention therapies improves long-term adherence [16], more patients in the wake of SPARCL are having statins initiated soon after symptom onset. Studies evaluating the effects of hyperlipidemia and early statin therapy on

AIS outcomes have shown mixed results. In the Lausanne stroke database, patients with hypercholesterolemia were twice as likely to have *better* functional outcomes than those with normal cholesterol and had less mortality [17]. Early statin treatment was not beneficial in a pilot trial [18], whereas the trial of Colivicchi et al. [19] suggests that discontinuation of statins is harmful. Statin use was associated with a small risk of ICH in 2 controlled, randomized trials enrolling many stroke patients, although the treatment benefits outweighed the risks [11, 20]. A study of IVF-treated patients suggests that early statin therapy is associated with improved outcomes 3 months after stroke [21]. This study found no relationship between ICH and statin use, although more recent research shows that low total cholesterol level may be associated with symptomatic ICH [22]. No prior studies have investigated the effects of baseline lipid levels and peri-incident statin use on AIS outcomes after endovascular recanalization therapy. Since ICH is the main concern of IAF and PME, it is crucial to know whether statins may pose an additional risk to treated individuals. In this study, we analyze the impact of hyperlipidemia and statin use before and after AIS treated with IAF and PME, as well as the relationship between hyperlipidemia on functional, neurologic, and angiographic outcomes.

Methods

General Comment and Entry Criteria

This is an analysis of a prospectively maintained computer database of patients treated with IAF and PME at the University of California, Los Angeles, Medical Center from 1992 to 2006. Data entry and analysis was approved by the local institutional review board. We included patients meeting the following criteria: (a) treatment with endovascular recanalization procedures within 12 h of AIS onset, (b) minimal or absent perfusion of the apparent symptom-related vessel upon initiation of the endovascular procedure, and (c) available information regarding pharmacological therapy before and after symptom onset. Patients enrolled in formal clinical trials and those treated in routine clinical practice were included. Patients treated in formal trials met the entry criteria for those studies. Subjects examined in routine practice were treated either on label according to FDA instructions for use or off label whenever the attending vascular neurologist and interventional neuroradiologist both felt that therapy offered better chances of a good outcome. Informed consent for intervention was obtained from the patient or a legally authorized representative. Relative contraindications to intervention were: (a) significant spontaneous neurological recovery, (b) systolic blood pressure (SBP) greater than 185 mm Hg and diastolic blood pressure (DBP) greater than 110 mm Hg, not controlled by medical therapy at the start of the procedure, (c) ICH, and (d) mass effect on neuroimaging.

Endovascular Procedures and Assessment of Degree of Revascularization

IAF and PME protocols are described in detail elsewhere [8–10]. IAF was carried out with either prourokinase or rt-PA. PME was performed using the Merci Clot Retrieval Device, which was advanced through a microcatheter and allowed to regain helical shape once delivered distal of the arterial occlusion, thereby ensnaring the embolus. This routine was repeated up to 6 times in case of persistent occlusion. Revascularization was determined by the operating radiologist using the Thrombolysis in Myocardial Infarction (TIMI) classification [23].

Assessment of Functional Outcomes, Lipid Panel and Stroke Etiology

Neurological deficits were quantified by a neurologist using the National Institutes of Health Stroke Scale (NIHSS) on all patients prior to the procedure and on day 7 after admission (or at discharge, if before 7 days). Functional outcomes were rated using the modified Rankin score (mRS) at discharge and on day 90, either by one of the investigators during a follow-up with each patient or by a trained research assistant during a telephone interview. We defined 'excellent functional outcome' as mRS of 0 or 1, 'poor functional outcome' as mRS of 2–6, and 'neurological improvement' as NIHSS decline equal to or greater than 4 points 7 days or less after the procedure, provided that the resulting NIHSS score did not exceed 10. Successful recanalization was defined as TIMI score of 2–3, whereas TIMI 0–1 was deemed unsuccessful. We termed symptomatic ICH as any acute intraparenchymal bleeding associated with neurological worsening of 4 or more points over the baseline NIHSS score. The stroke etiology was determined by a neurologist, after reviewing the available workup. All patients received head CT or brain MRI immediately after the endovascular procedure to monitor for ICH. History of hyperlipidemia (history of elevated cholesterol and/or triglycerides) was obtained from the patient's self-report or available medical records. The fasting lipid panel was collected the morning after hospital admission and was comprised of LDL, high-density lipoprotein cholesterol, total cholesterol, triglyceride, and non-high-density-lipoprotein-cholesterol levels.

Statistical Analyses

Unadjusted analyses were performed using exact χ^2 tests for binary outcomes and Wilcoxon rank sum tests for continuous outcomes. Multivariate analyses included logistic regression for binary outcomes, whereas linear regression was used for continuous outcomes. Preliminary bivariate analyses were conducted as the first step in variable selection for all outcomes. To obtain the final set of predictors we used a backwards stepwise variable selection procedure with a $p < 0.25$ retention criterion. The outcome analysis was controlled for the following factors: age, gender, severity of neurologic deficits (determined by NIHSS), successful recanalization, premorbid functional status (determined by mRS), LDL level, SBP and DBP on admission, stroke etiology (large-artery atherosclerosis or cardioembolism), total cholesterol level, glucose level on admission, and history of hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, atrial fibrillation and smoking. The variables for SBP, DBP and admission glucose level were analyzed in continuous and binary forms, using cutoff values of 180 mm Hg, 110 mm Hg and 200 mg/dl, respectively. Analyses relating to hemorrhagic events were adjusted for the following covariates: age,

SBP, DBP, glucose on admission, initial NIHSS score, history of diabetes, atrial fibrillation, cholesterol level, LDL, successful recanalization, IVF pretreatment, IAF, use of Merci, INR on admission, platelet count on admission, antiplatelet therapy, and warfarin use before stroke. Significance was set at the $p \leq 0.05$ level. A statistical trend was considered for p values of 0.05–0.19.

Results

The entry criteria were met by 142 patients, whose characteristics are summarized in table 1. IAF was performed in 113 patients (80%) and PME in 32 patients (22%). Combined intravenous (0.6 mg/kg) and intra-arterial rt-PA was used in 37 (26%), intra-arterial rt-PA alone in 40 (28%), intra-arterial prourokinase alone in 33 (23%), PME alone in 27 (19%), combined intravenous rt-PA and PME in 2 (2%), and combined intra-arterial rt-PA and PME in 3 patients (2%). Revascularization procedures were initiated on average 7.1 h after symptom onset (range = 1.5–10). Lesions mostly involved the anterior circulation (15 cases had lesions in the vertebrobasilar circulation). Successful recanalization was attained in 112 patients (71% of total). About half of the patients were admitted to our hospital prior to 2001, when service policy was initiating statins when indicated by the guidelines of the National Cholesterol Education Program II; thereafter, service policy was initiating statins whenever the ischemic events were due to large- or small-vessel atherothromboembolic disease or if the patients had CAD or coronary risk equivalent indication for statin therapy [16]. Before AIS, 22 patients were on statins (mostly atorvastatin, $n = 10$; median = 20 mg/day; range = 5–80 mg/day). The majority of these patients continued receiving statins after hospital admission (21/22), whereas statins were initiated in 45 additional patients after admission. Most patients treated with statins in the hospital received atorvastatin ($n = 32$; median = 10 mg/day; range = 10–80 mg/day). Statin therapy was instituted within 48 h after admission in 50 patients and postponed for 2–19 days in 16. Excellent functional outcomes were obtained in 45 patients (32%). Death occurred in 19 (13%) cases within 1 month after the procedure, increasing to 33 (23%) at 3 months.

In univariate analyses, statin therapy prior to stroke was not related to recanalization rates, mortality or excellent functional outcome (both at discharge and after 3 months). Unadjusted analyses showed that elevated total cholesterol, advanced age, hypertension, as well as increased SBP, DBP, pretreatment NIHSS and glucose were less frequently associated with excellent functional status at 3 months (table 2). There were no significant differ-

Table 1. Patient characteristics

Variable	All patients (n = 142)	No statins (n = 75)	Statins after (n = 45)	Statins before and after (n = 21)	p value
Age, years	68.7 ± 17	66.7 ± 18.2	69.2 ± 15.3	74.3 ± 13	NS
Male gender	73 (51)	35 (47)	27 (60)	11 (52)	NS
IAF	112 (79)	65 (89)	28 (70)	18 (82)	0.0043
Bridging IVF	37 (26)	11 (15)	8 (18)	6 (29)	NS
PME	32 (22)	11 (15)	18 (40)	3 (14)	0.0057
Risk factors					
Hypertension	96 (68)	47 (63)	30 (67)	18 (86)	NS
DM	15 (11)	5 (7)	3 (7)	7 (33)	0.0060
CAD	45 (32)	30 (47)	10 (22)	15 (71)	NS
Hyperlipidemia	44 (31)	15 (21)	12 (27)	16 (76)	<0.0001
Atrial fibrillation	31 (22)	16 (21)	12 (27)	3 (14)	NS
Smoking	26 (18)	15 (21)	7 (16)	3 (14)	NS
Cerebrovascular disease	29 (20)	21 (28)	7 (15.5)	7 (33)	NS
Treatment before					
Antiplatelet	50 (35)	23 (32)	12 (27)	15 (71)	0.0017
Warfarin	13 (9)	7 (10)	2 (4)	3 (14)	NS
Etiology					
LAA	35 (25)	21 (33)	7 (26)	7 (39)	NS
CE	50 (35)	28 (44)	14 (52)	8 (44)	NS
Pretreatment clinical characteristics					
SBP	156 ± 30	156 ± 32	156 ± 24.5	156 ± 33	NS
DBP	83 ± 18	83 ± 19	86 ± 17	77 ± 21	NS
Cholesterol	170 ± 39	164 ± 32	181 ± 40	179 ± 42	0.043
LDL	106 ± 31	101 ± 28	117 ± 31	92 ± 29	0.0054
Glucose	139 ± 61	140 ± 73	136 ± 45	144 ± 47	NS
NIHSS	17 ± 7	19 ± 7	15 ± 7	14 ± 6	0.0932
mRS 0–1	138 (97)	70 (99)	39 (97.5)	17 (90)	NS

Figures are means ± SD or numbers of cases with percentages in parentheses. No statins: Patients never receiving statins; Statins after: patients receiving Statins *only* after stroke; Statins before and after: patients on statins before stroke, kept on statins thereafter. NS = Nonsignificant; LAA = large-artery atherosclerosis; CE = cardioembolism.

ences in recanalization rates, mortality or functional outcome (at discharge and after 3 months) between patients treated with statins and those not receiving statins before AIS. Patients never receiving statins exhibited a trend toward having severer neurological deficits 7 days after symptom onset or at discharge than those treated with statins before or only after AIS (NIHSS score of 15.5 ± 14 for patients not receiving statins versus 9.5 ± 16 and 11 ± 18 for those on statins before and before and after stroke, respectively, $p = 0.0871$). However, the premorbid characteristics of the patients on statins differed from those who did not receive such treatment. The patients receiving statins before and after AIS had more comorbid conditions (particularly DM and hyperlipidemia) and were older than the controls.

On multivariate analysis (table 3), age, NIHSS and higher total cholesterol level were independent predictors

of excellent outcome at 3 months. An increase in total cholesterol of 50 mg/dl was associated with a 64% decrease in the odds of having an excellent functional status at 3 months (OR = 0.36, 95% CI = 0.45–0.88, $p = 0.0253$). Trends were noted toward increased odds of an excellent functional status at 3 months in patients receiving statins after AIS and in patients who were given statins before and after the stroke, compared to those who never received such therapy. After adjusting for total cholesterol level, the association between statin use and excellent functional outcomes at 3 months was weakened (statin use after vs. never: OR = 1.7, 95% CI = 0.5–6.6; statin use before and after versus never: OR = 0.7, CI = 0.1–3.6). Patients using statins before and after AIS had lower total cholesterol levels on average compared to those who never used statins.

Fifty-six patients (39% of total) experienced neurological improvement within 7 days after the procedure. Ad-

Table 2. Predictors of excellent functional outcome at 3 months

Effect	p value	OR	Lower limit	Upper limit
Age	0.0006	0.653	0.512	0.833
LDL	0.5200	0.785	0.375	1.641
SBP	<0.0001	0.129	0.050	0.336
NIHSS on admission	0.0011	0.356	0.191	0.662
Total cholesterol	0.2885	0.716	0.387	1.326
Blood glucose	0.0171	0.480	0.262	0.879
LAA (yes vs. no)	0.0861	0.441	0.173	1.124
DM (yes vs. no)	0.0672	0.143	0.018	1.147
Hypertension (yes vs. no)	0.0005	0.231	0.102	0.525
Total cholesterol (high vs. low)	0.1087	0.490	0.205	1.171

OR relate to increases in age of 10 years, LDL of 50 units, SBP of 50 units, NIHSS of 10 units, total cholesterol of 50 units, DBP of 20 units and glucose of 50 units. LAA = Large-artery atherosclerosis.

Table 3. Predictors of excellent functional outcome at 3 months

Effect	Point estimate	95% Wald		p value
		confidence	limits	
Statin use after versus never	2.091	0.714	6.130	0.1787
Statin use B + A versus never	3.215	0.573	18.032	0.1843
SBP >180 mm Hg	0.124	0.012	1.238	0.0754
History of diabetes	0.117	0.010	1.359	0.0863
Glucose level on admission, mg/dl	0.991	0.979	1.005	0.1985
Age (per year)	0.956	0.927	0.986	0.0041
Male gender	1.986	0.733	5.380	0.1771
Baseline NIHSS (per point)	0.881	0.812	0.957	0.0025
High cholesterol	0.284	0.082	0.988	0.0478

OR for a 1-unit increase for continuous variables of glucose, age and NIHSS on admission.

vanced age, history of hypertension, and elevated NIHSS score and blood pressure on admission were associated with worse neurological deficits 7 days after admission or at hospital discharge on bivariate analyses. After adjusting for covariates, history of hyperlipidemia was related to an average 4.6-unit increase in NIHSS (standard error = 2.28, $p = 0.0462$). Patients receiving statins after AIS were more likely to have neurological improvement compared to those never using statins (44 vs. 25%, $p = 0.056$). Neurological improvement occurred in 45% of the statin users before and after stroke but only in 39% of those never using statins ($p = 0.2015$). Statin therapy before and after stroke resulted in a significant 6.5-point NIHSS decrease at discharge on average, compared to patients not receiving statins ($p = 0.0168$). Statin use after AIS was as-

sociated with an average 4.2-unit NIHSS score improvement ($p = 0.056$).

Bivariate analyses indicated that unsuccessful recanalization was significantly linked with glucose greater than 200 mg/dl (OR = 0.7, 95% CI = 0.51–0.99; $p = 0.0477$) and NIHSS score on presentation (OR = 0.49, 95% CI = 0.28–0.86; $p = 0.0141$). In adjusted analyses, statin use before therapy did not alter the odds of successful recanalization (statin use before and after versus never: OR = 1.5, 95% CI = 0.3–6.3). Severe extracranial hemorrhage was rare, with 3 patients experiencing this complication. However, surveillance neuroimaging showed postprocedural ICH in 39 patients (27% of total), 22 of which deteriorated neurologically (15% of total). Unadjusted analyses did not reveal significant differences between statin

groups regarding systemic or intracranial hemorrhage risk. Bivariate scrutiny revealed that admission NIHSS score and previous warfarin use were significantly associated with an increased risk of systemic hemorrhage, whereas ICH was related to initial stroke severity and glucose levels ≥ 200 mg/dl. After adjusting for covariates, statin use remained unrelated to systemic bleeding (statin use after vs. never: OR = 1.5, 95% CI = 0.6–4.0; statin use before and after vs. never: OR = 1.4, 95% CI = 0.4–4.9) or any ICH (statin use after vs. never: OR = 1.5, 95% CI = 0.5–4.1; statin use before and after vs. never: OR = 2.3, 95% CI = 0.7–8.2). Increased SBP, NIHSS and glucose levels on admission, as well as DM, were associated with increased risk of symptomatic ICH on bivariate analyses. Statin use *before and after* AIS was not associated with symptomatic ICH (OR = 1.1, $p = 0.87$).

Conclusions

Our analysis of a prospective cohort of AIS patients treated with endovascular procedures suggests that higher serum cholesterol levels at presentation were related to worse final functional outcomes, while therapy with statins before and after symptom onset was associated with better outcomes. To our knowledge, this is the first study addressing the impact of cholesterol levels and statin use on functional outcomes after IAF and PME. Our initial aim was to test the hypothesis that statin use before AIS leads to better angiographic and neurological outcomes, given that statins reduced the cerebral infarction size by almost 50% in a murine model of ischemic stroke [24, 25]. This effect is mediated by endothelial nitric oxide synthase upregulation leading to global augmentation of the cerebral blood flow. Statins also induced angiogenesis, neurogenesis and synaptogenesis in rats subjected to intraluminal cerebral artery occlusion, resulting in enhanced recovery [26]. Some suggest parallel effects in humans, since statin use before stroke has been associated with better outcomes in patients treated with or without IVF [21, 27–29]. We reasoned that the study of patients undergoing acute endovascular recanalization could provide additional insights into the effects of statin therapy because of detailed clinical and angiographic information before and after the intervention.

In this study, statins were associated with mild benefits on neurologic outcomes. These benefits were not mediated via promotion of recanalization, as statin therapy did not influence postprocedural vessel patency. This suggests at least 2 possibilities: first, that statins increased

the cerebral blood flow through available collaterals improving regional brain microcirculation irrespective of recanalization; second, that neuroprotection and subsequent neuronal plasticity was favored independently of improved cerebral perfusion [26, 27]. Both speculations are plausible based on results of murine experiments [24, 26]. Alternatively, trends toward benefit from pretreatment statin therapy may reflect type II error or confounding effects of unmeasured variables that distinguish statin- and non-statin-treated patients.

SPARCL results have stimulated statin use in AIS, notwithstanding the mild ICH excess noted in the active treatment arm [11, 12]. ICH is also the main concern related to IAF and PME and is more frequent with endovascular procedures than IVF. Therefore, it is necessary to know whether AIS patients undergoing endovascular procedures incur in further risks when concomitantly treated with statins. However, we detected no significant difference in symptomatic ICH rates between patients receiving statins and those not treated with such medications, in accord with a prior study of patients treated with intravenous rt-PA [20] and a report suggesting that the functional outcomes improve if statins are started within 4 weeks after AIS [29].

This study has limitations. Different statins were used, although atorvastatin predominated. The small number of patients taking each individual statin prevents meaningful analysis of possible advantages of a given drug over its counterparts. Although statins share the same cholesterol-lowering mechanism, they have dissimilar pharmacological properties (i.e. anti-inflammatory effects and blood-brain barrier penetration) [25]. Also, the statin dosages were variable and most patients received them at low to moderate doses. Evidence suggests that high doses confer greater clinical benefits [11, 24, 25]. Finally, we could have incurred referral bias, given the complexity of the cases. In conclusion, elevated cholesterol levels may decrease the odds of excellent functional outcomes in AIS patients treated with endovascular procedures, whereas the prognosis may be more favorable for patients receiving statins before and after stroke onset. These findings need to be confirmed in independent and larger data sets.

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