

# Lipid Profile, Lipid-lowering Medications, and Intracerebral Hemorrhage After tPA in Get With The Guidelines–Stroke

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**Background and Purpose**—Symptomatic intracerebral hemorrhage (sICH) after tissue plasminogen activator for acute ischemic stroke is associated with poor outcome. There are conflicting data on sICH risk related to lipid levels and use of lipid-lowering medications. We evaluated whether there are associations between lipid levels, lipid-lowering medications, and sICH in Get With the Guidelines–Stroke.

**Methods**—We identified acute ischemic stroke patients in the Get With the Guidelines–Stroke data set who were treated with IV tissue plasminogen activator between April 2003 and September 2009 and had complete data on lipid profiles and complications. Potential predictors of sICH were tested in univariate and multivariate analysis.

**Results**—The analysis included 22 216 IV tissue plasminogen activator–treated acute ischemic stroke patients. Overall, 1104 (4.97%) experienced sICH (National Institute of Neurological Disorders and Stroke definition). In univariate analysis, patients with sICH were more often taking antihypertensive, lipid-lowering, and diabetes mellitus medications. There was no relationship between low density lipoprotein or total cholesterol and sICH in univariate analysis. However, the risk of sICH increased with higher high density lipoprotein, 6.1% in Q4 versus 4.7% in Q1,  $P=0.0013$ ; and lower triglyceride levels, 5.9% in Q1 versus 4.2% in Q4,  $P<0.0001$ . In multivariable models, although the high density lipoprotein and triglyceride levels were modestly associated with sICH, low density lipoprotein and total cholesterol were not. Lipid-lowering medications were not independently associated with sICH.

**Conclusions**—We found that low density lipoprotein and total cholesterol levels are not associated with risk of sICH after tissue plasminogen activator, although higher high density lipoprotein and lower triglyceride levels were modest risk factors. Lipid-lowering medications are not associated with risk of sICH. (*Stroke*. 2013;44:1354-1359.)

**Key Words:** hemorrhage ■ lipid-lowering medication ■ lipids ■ stroke ■ tissue plasminogen activator

Tissue plasminogen activator (tPA) improves outcome from acute ischemic stroke in select patients.<sup>1</sup> However, neurological deterioration associated with intracerebral hemorrhage (ICH) is associated with poor outcome, and the mortality rate approaches 75% at 3 months.<sup>2,3</sup> Previous studies of patients who have received tPA for stroke have elucidated multiple clinical and demographic predictors of symptomatic ICH (sICH).<sup>2,4–8</sup> There have been conflicting studies that have looked for an association among lipid levels, lipid-lowering medication, and brain hemorrhages, and it is uncertain whether these factors affect the decision to treat an individual patient with tPA.<sup>9–18</sup>

Get With The Guidelines–Stroke (GWTG–Stroke) program was undertaken by the American Heart Association/American Stroke Association (AHA/ASA) as a national quality

improvement initiative to advance the treatment of patients with stroke and transient ischemic attack. We evaluated the relationship among lipid subtypes, lipid-lowering medications, and risk of sICH after tPA in GWTG–Stroke.

## Methods

The GWTG–Stroke data set has been described extensively in previous publications.<sup>19,20</sup> In brief, trained hospital personnel were instructed to ascertain consecutive patients admitted with acute ischemic stroke by either prospective clinical identification, retrospective identification using *International Classification of Diseases Ninth Revision (ICD-9)* discharge codes, or a combination. Methods used for prospective identification varied but included regular surveillance of emergency department records (ie, presenting symptoms and chief complaints), ward census logs, or neurological consultations. The eligibility of each acute stroke admission was confirmed at chart review before abstraction. The quality of GWTG–Stroke data has been compared

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with chart abstraction by trained auditors and demonstrated to have a very high overall composite accuracy rate.<sup>21</sup> Data from hospitals that participated in the program at any time between April 2003 and September 2009 were included in this analysis. All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Outcome Sciences, Inc (Cambridge, MA) served as the registry coordinating center. The Duke Clinical Research Institute (Durham, NC) served as the data analysis center, and institutional review board approval was granted to analyze aggregate deidentified data for research purposes.

We queried the GWTG-Stroke data set to identify acute ischemic stroke patients who were treated with IV tPA during a period extending from April 2003 through September 2009 (n=42 078 patients treated at 1014 hospitals). Patients who received an experimental thrombolytic, intra-arterial tPA, or IV tPA at an outside, non-GWTG-Stroke hospital were excluded (n=12 967). Patients for whom key data of interest were missing, including complications of thrombolysis and full lipid profiles, were also excluded (n=6057 missing the lipid profile and n=838 missing complications data). The primary outcome of interest was the rate of symptomatic intracerebral hemorrhage (sICH) within the first 36 hours of treatment defined as any neurological deterioration with evidence of hemorrhage on repeat brain imaging (National Institute of Neurological Disorders and Stroke definition).

Potential predictors of sICH, including demographic, clinical, and laboratory variables, were tested in univariate analysis using  $\chi^2$  test for categorical variables and the Wilcoxon rank sum test for continuous variables. Univariate tests of association between components of the lipid profile and risk of sICH were conducted using separate logistic regression models with generalized estimating equations to account for clustering within hospitals. Multivariable logistic regression modeling was then performed to identify the components of the lipid profile independently associated with sICH, again using generalized estimating equations to account for clustering within hospitals. All multivariable models were adjusted for age, gender, race, medical history (coronary artery disease/prior myocardial infarction, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation/flutter, previous stroke, previous transient ischemic attack, smoking, carotid stenosis, peripheral vascular disease), prior antithrombotic, antihypertensive, lipid-lowering, or diabetic medication, and hospital characteristics (region, academic versus nonacademic, number of beds). Multivariable models included all 4 lipid profile components, including total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (TRGs), to examine their independent contributions. Data were missing in <7% of patients except for initial National Institutes of Health Stroke Scale (NIHSS) (16%); therefore, multivariable models were performed with and without NIHSS. Missing information on all other covariates was imputed using the most common value. All statistics were performed using SAS version 9.1 software (SAS Institute, Cary, NC).

## Results

The GWTG-Stroke database includes information on 22 216 acute ischemic stroke patients treated with IV tPA with complete data on lipid profiles and hemorrhagic complications. Table 1 presents the clinical, demographic, and hospital characteristics of patients with lipid data compared with those without. Patients without lipid data were older, more likely to have atrial fibrillation, and had more severe strokes based on higher NIHSS scores, sICH rate, and in-hospital mortality compared with patients with lipid data. Among those patients included in the analysis, sICH occurred in 1104 (4.97%). Table 2 provides clinical and demographic data for patients included in this analysis, dichotomized by whether or not the patient developed sICH. In univariate analysis, patients with sICH were older, had more severe strokes, and more often had

medical comorbidities including coronary artery disease, diabetes mellitus, hypertension, and atrial fibrillation, but were less often active smokers. Patients with sICH were more often taking antihypertensive, lipid lowering, and diabetes mellitus medications.

In univariate analysis, total cholesterol and LDL levels were not associated with sICH (Table 3). However, the risk of sICH increased in the uppermost quartile of HDL (6.1% in Q4 vs 4.7% in Q1;  $P=0.0013$ ), and with lower TRG levels (5.9% in Q1 vs 4.2% in Q4;  $P<0.0001$ ). In the multivariable model without NIHSS, the TRG levels were independently associated with sICH, and HDL trended to an association; in the multivariable model with NIHSS, both the HDL and TRG levels were independently associated with sICH (Table 4). These associations were present and remained significant among patients with diabetes mellitus versus without, and those taking lipid-lowering medications before admission (data not shown) versus those not taking. Furthermore, use of lipid-lowering agents was not associated with sICH either in an adjusted model incorporating the previously discussed covariates (including NIHSS) and lipid subtypes (odds ratio [OR], 1.09; 95% confidence intervals [CI], 0.92–1.29) or in a model in which lipid subtypes were not included (OR, 1.04; 95% CI, 0.89–1.23). Performing the same analysis evaluating the relationship between lipid-lowering drugs and sICH without NIHSS as a covariate yielded similar results in the model including lipid subtypes (OR, 1.11; 95% CI, 0.95–1.29) and the model excluding lipid subtypes (OR, 1.06; 95% CI, 0.91–1.22). Finally, a sensitivity analysis was performed to determine the effect of imputation of missing data using 85% of the sample with data for lipids and all covariates excluding NIHSS, and the results were not meaningfully changed (data not shown).

## Discussion

This analysis of a large cohort of acute stroke patients who received IV tPA in clinical practice found no relationship between sICH and total cholesterol or LDL levels, whereas higher HDL and lower TRG were associated with a modestly increased risk of sICH. Multiple population-based studies have identified an association between low total cholesterol and primary ICH, but specific lipid subtypes were not evaluated.<sup>9–11</sup> The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) randomized study of atorvastatin for secondary stroke prevention found no relationship between the baseline levels of either total or LDL cholesterol and the risk of hemorrhagic stroke, no interaction between baseline cholesterol levels and risk of bleeding with statin treatment, and no independent effect of LDL cholesterol levels at the last measurement before a hemorrhagic stroke in those treated with atorvastatin.<sup>16</sup> Furthermore, there is evidence from a large population-based MRI study that lower TRG is associated with increased risk for primary ICH and prevalence of cerebral microbleeds, whereas LDL had no association.<sup>22</sup>

Focusing only on acute ischemic stroke patients, 2 previous publications identified lower LDL level as an independent predictor of hemorrhage in patients with acute ischemic stroke. The first involved only 104 patients who received thrombolysis and did not adjust for other lipid subtypes.<sup>12</sup> The second study

**Table 1. Clinical and Demographic Characteristics of Patients Included in the Analysis Compared With Those Excluded Due to Missing Lipid Data**

	Overall (n=27 928)	With Lipid Data (n=22 216)	Without Lipid Data (n=5712)	P Value
Age, y*	69.9±14.7	69.4±14.6	71.4±14.8	<0.0001
Female	49.7%	48.9%	52.8%	<0.0001
Nonwhite	20.6%	21.2%	18.4%	<0.0001
Hypertension	76.4%	76.6%	75.8%	0.21
Diabetes mellitus	25.2%	24.8%	26.7%	0.0054
Dyslipidemia	39.0%	39.2%	38.4%	0.32
Atrial fibrillation	23.9%	22.7%	28.4%	<0.0001
Coronary artery disease	29.8%	29.1%	32.6%	<0.0001
Active smoker	20.7%	21.3%	18.2%	<0.0001
Prior stroke	4.1%	4.2%	3.8%	0.21
Prior TIA	2.2%	2.2%	2.0	0.32
Initial NIHSS†	12 (7–18)	12 (7–18)	13 (8–19)	<0.0001
Rate of sICH	5.7%	5.0%	8.2%	<0.0001
In-hospital mortality	9.6%	7.8%	16.6%	<0.0001
Prior medications				
Antithrombotic	45.6%	45.0%	47.6%	<0.0001
Antihypertensive	65.1%	65.3%	64.2%	0.0002
Lipid lowering	35.7%	35.5%	36.1%	0.0009
Diabetic	18.1%	17.8%	19.0%	<0.0001
Hospital Characteristics				
Region				<0.0001
Northeast	28.4%	27.8%	30.9%	
Midwest	17.7%	17.9%	16.9%	
South	33.2%	33.6%	31.5%	
West	20.7%	20.6%	20.7%	
Nonacademic	37.0%	36.3%	39.7%	<0.0001
Number of beds†	380 (266–564)	394 (274–572)	356 (247–520)	<0.0001

sICH indicates symptomatic intracerebral hemorrhage; and TIA, transient ischemic attack.

\*Mean±SD.

†Median (interquartile range).

evaluated a cohort of 377 patients with acute ischemic stroke, of whom only 10% had received a thrombolytic, and found that lower LDL was associated with hemorrhagic transformation in patients with stroke because of large artery atherosclerosis but not cardioembolic stroke.<sup>13</sup> Subsequently, multiple studies have found no association between LDL and sICH after thrombolysis for ischemic stroke.<sup>14,15,23</sup> A study of 252 patients treated with IV tPA noted an opposite effect of TRG; higher TRG was associated with a higher risk of sICH in multivariable analysis, but our study is substantially larger.<sup>14</sup> Finally, a recent multicenter observational study of ≈2500 patients who received IV tPA for acute stroke in clinical practice found no significant association between any of the 4 primary lipid subtypes and sICH.<sup>23</sup> However, this study lacked the statistical precision to rule out a small effect and the CI overlap with the results from our much larger study. Taking all of these studies together with our findings, the risk of sICH after thrombolysis does not seem to be affected by low levels of the cardinal atherogenic lipid subtype of LDL, whereas there is a possibility that HDL and TRG levels mildly promote sICH. The reason for this latter finding is not certain, but there is evidence that higher TRGs may prevent

hemorrhages because they are positively correlated with the vitamin K–dependent coagulation factors VII and IX, and with plasminogen activator inhibitor and blood viscosity.<sup>24</sup>

In this cohort, we did not identify an independent contribution to increased risk of sICH from use of lipid-lowering medication. GWTG-Stroke does not capture the type of lipid-lowering agent being taken by each patient, but statins are clearly the most commonly prescribed class of medication for cholesterol reduction. As of 2002, statins accounted for 87% of lipid-lowering medications prescribed to patients in the United States.<sup>25</sup> Statins have modest antithrombotic effects, and it is possible that this could contribute to sICH after tPA.<sup>26</sup> There is evidence from the SPARCL randomized trial that high dose statins are associated with primary ICH in patients with previous stroke.<sup>16</sup> However, the risk of ICH in SPARCL was largely seen in patients who had entered the study with a primary ICH, and subsequent meta-analyses of statin studies have not identified an association with ICH.<sup>17</sup> Only 1 cohort of 311 patients who received intra-arterial tPA noted an increased risk of any ICH among those patients on a statin.<sup>15</sup> Several other previously published cohorts have

**Table 2. Clinical, Demographic, and Hospital Characteristics of Patients Included in This Analysis, Dichotomized With and Without sICH**

	Overall (n=22 216)	With sICH (n=1104)	Without sICH (n=21 112)	P Value
Age, y*	69.4±14.6 [22 216]	73.6±12.5 [1104]	69.2±14.7 [21 112]	<0.0001
Female	48.9% (10 861) [22 206]	47.0% (519) [1103]	49.0% (10 342) [21 103]	0.21
Nonwhite	21.2% (4708) [21 439]	23.4% (258) [1064]	21.1% (4450) [20 375]	0.064
Hypertension	76.6% (15 826) [20 662]	80.9% (857) [1059]	76.4% (14 969) [19 603]	0.0006
Diabetes mellitus	24.8% (5130) [20 662]	30.0% (318) [1059]	24.6% (4812) [19 603]	<0.0001
Dyslipidemia	39.2% (8094) [20 662]	39.8% (421) [1059]	39.1% (7673) [19 603]	0.69
Atrial fibrillation	22.7% (4688) [20 662]	30.2% (320) [1059]	22.3% (4368) [19 603]	<0.0001
Coronary artery disease	29.1% (6010) [20 662]	34.4% (364) [1059]	28.8% (5646) [19 603]	0.0001
Active smoker	21.3% (4398) [20 662]	14.7% (156) [1059]	21.6% (4242) [19 603]	<0.0001
Previous stroke	4.2% (866) [20 662]	3.5% (37) [1059]	4.2% (829) [19 603]	0.24
Previous TIA	2.2% (457) [20 662]	1.8% (19) [1059]	2.2% (438) [19 603]	0.34
Carotid stenosis	3.3% (684) [20 662]	3.1% (33) [1059]	3.3% (651) [19 603]	0.72
Peripheral vascular disease	3.8% (793) [20 662]	4.5% (48) [1059]	3.8% (745) [19 603]	0.23
Initial NIHSS†	12 (7–18) [18 653]	16 (10–21) [927]	11 (7–17) [17 726]	<0.0001
<b>Prior Medications</b>				
Antithrombotic	45.0% (10 005) [21 192]	51.3% (566) [1049]	44.7% (9439) [20 143]	<0.0001
Antihypertensive	65.3% (14 503) [21 411]	72.5% (800) [1046]	64.9% (13 703) [20 365]	<0.0001
Lipid lowering	35.5% (7896) [21 345]	40.0% (441) [1063]	35.3% (7455) [20 282]	0.0018
Diabetic	17.8% (3962) [21 922]	21.4% (236) [1086]	17.7% (3726) [20 836]	0.0013
<b>Hospital Characteristics</b>				
Region	[22 216]	[1104]	[21 112]	0.15
Northeast	27.8% (6176)	27.3% (301)	27.8% (5875)	
Midwest	17.9% (3983)	17.8% (197)	17.9% (3786)	
South	33.6% (7474)	36.4% (402)	33.5% (7072)	
West	20.6% (4583)	18.5% (204)	20.7% (4379)	
Nonacademic	36.3% (8062) [22 216]	36.0% (397) [1104]	36.3% (7665) [21 112]	0.82
Number of beds†	394 (274–572) [22 216]	399 (263–576) [1104]	394 (274–572) [21 112]	0.52

Values in brackets are the number of patients with data. sICH indicates symptomatic intracerebral hemorrhage; and TIA, transient ischemic attack.

\*Mean±SD.

†Median (interquartile range).

**Table 3. Univariate Analysis of the Risk of sICH for Each Lipid Subtype by Quartile**

Lipid Subtype	Quartile End Points, mg/dL	sICH Rate	P Value
<b>LDL</b>			
Quartile 1	30 to <76	5.3% (289/5462)	0.23
Quartile 2	76 to <98	5.1% (281/5474)	
Quartile 3	98 to <125	4.6% (262/5701)	
Quartile 4	125–401	4.9% (272/5579)	
<b>HDL</b>			
Quartile 1	3 to <34	4.7% (246/5248)	0.0013
Quartile 2	34 to <42	4.5% (261/5747)	
Quartile 3	42 to <51	4.4% (236/5329)	
Quartile 4	51–100	6.1% (361/5892)	
<b>Triglycerides</b>			
Quartile 1	5 to <73	5.9% (324/5448)	<0.0001
Quartile 2	73 to <102	5.3% (291/5541)	
Quartile 3	102 to <147	4.5% (254/5599)	
Quartile 4	147–1881	4.2% (235/5628)	
<b>Cholesterol</b>			
Quartile 1	14 to <139	5.5% (295/5378)	0.42
Quartile 2	139 to <165	4.8% (266/5566)	
Quartile 3	165 to <196	4.9% (282/5699)	
Quartile 4	196–817	4.7% (261/5573)	

HDL indicates high density lipoprotein; LDL, low density lipoprotein; and sICH, symptomatic intracerebral hemorrhage.

found no increased risk of sICH in patients taking statins when given thrombolytics for stroke.<sup>18,27–29</sup> A recent meta-analysis that included 3 of these cohorts did report an increased risk of sICH in patients on a statin, with an OR of 1.99 (95% CI, 1.03–3.84).<sup>18</sup> However, this meta-analysis did not include patient level data, and thus multivariable risk factor adjustment was not performed. Finally, a pooled observational study of 11 databases including >4000 acute stroke patients treated with IV tPA found no significant association between sICH or outcome after adjusting for potential confounders.<sup>30</sup> Our results, which include a much greater number of patients and an extensive multivariable analysis, confirm that lipid-lowering medications are not independently associated with sICH.

GWTG-Stroke includes a very large cohort of acute stroke patients treated with thrombolysis in clinical practice, thus providing excellent power to detect associations. However, there

are important limitations to this study. Key data were missing in a substantial portion of patients, primarily lipid profiles, which possibly introduced a systematic bias that affected our results. Patients without lipid data were older, had more atrial fibrillation, and had more severe strokes, and thus our results should be interpreted cautiously because they may not be representative of all stroke patients. Importantly, other factors that we identified as having an association with sICH in the study cohort were similar to previous reports, including NIHSS, age, atrial fibrillation, diabetes mellitus, smoking, and hypertension, suggesting that our cohort is not atypical.<sup>2,4–6</sup> Many previous cohorts of stroke patients who received thrombolysis have identified serum glucose as a predictor of sICH.<sup>4,5,7,8</sup> Serum glucose at baseline was available for <25% of patients in the GWTG-Stroke data set, and history of diabetes mellitus was used as a surrogate, but there may have been residual confounding. As with other analyses of the GWTG-Stroke cohort, the data are dependent on the accuracy and completeness of clinical documentation and subsequent chart abstraction. Although quality of data has been demonstrated to be accurate compared with trained chart abstractors, there are no data addressing the validity of case ascertainment in GWTG-Stroke. Given the fact that this large data set has been used for multiple analyses, all analyses are secondary and should be considered hypothesis-generating only. Finally, residual measured and unmeasured confounding variables may have influenced the findings.

## Summary

We conclude that lipid-lowering medications are not associated with sICH, and use of these medications should not be a factor in deciding whether to treat acute stroke patients with thrombolytics. In addition, contrary to some previous reports, we did not find an association between LDL and sICH after thrombolysis. Instead, higher HDL and lower TRG were independently associated with a modest increased risk for sICH. Further research is needed to understand the underlying biology that might explain the increased risk observed in our study.

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**Table 4. Adjusted Odds Ratios for sICH by Lipid Subtype, With and Without NIHSS**

Lipid Subtype	Adjusted* Without NIHSS (1104 sICH in 22 216 cases)		Adjusted* With NIHSS (927 sICH in 18 653 cases)	
	OR (95% CI) Per 10 mg/dL Increase	P Value	OR (95% CI) Per 10 mg/dL Increase	P Value
LDL	1.00 (0.97–1.03)	0.82	1.01 (0.98–1.03)	0.54
HDL	1.04 (0.99–1.10)	0.12	1.06 (1.01–1.12)	0.025
Total cholesterol	1.03 (1.00–1.06)	0.048	1.02 (0.99–1.04)	0.14
Triglycerides	0.98 (0.97–0.99)	0.0025	0.99 (0.98–1.00)	0.019

CI indicates confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; OR, odds ratio; and sICH, symptomatic intracerebral hemorrhage.

\*Adjustment variables were age, gender, race, medical history (coronary artery disease/previous myocardial infarction, diabetes mellitus, hypertension, hyperlipidemia, atrial fib/flutter, previous stroke, previous transient ischemic attack, smoking, carotid stenosis, peripheral vascular disease), previous antithrombotic, antihypertensive, lipid lowering, or diabetic medication, and hospital characteristics (region, academic vs nonacademic, number of beds).

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