Serum Low-Density Lipoprotein Cholesterol Level Predicts Hematoma Growth and Clinical Outcome After Acute Intracerebral Hemorrhage

David Rodriguez-Luna, MD; Marta Rubiera, MD, PhD; Marc Ribo, MD, PhD; Pilar Coscojuela, MD; Jorge Pagola, MD, PhD; Socorro Piñeiro, MD; Bernardo Ibarra, MD; Pilar Meler, RN; Olga Maisterra, MD; Francisco Romero, MD, PhD; Jose Alvarez-Sabin, MD, PhD; Carlos A. Molina, MD, PhD

Background and Purpose—Lower serum low-density lipoprotein cholesterol (LDL-C) levels have been associated with increased risk of death after intracerebral hemorrhage (ICH). Nevertheless, their link with hematoma growth (HG) is unknown. Therefore, we aimed to investigate the relationship between LDL-C levels, HG, and clinical outcome in patients with acute ICH.

Methods—We prospectively studied 108 consecutive patients with primary supratentorial ICH presenting within 6 hours from symptoms onset. National Institutes of Health Stroke Scale score and ICH volume on computed tomography scan were recorded at baseline and at 24 hours. Lipid profile was obtained during the first 24 hours. Significant HG was defined as hematoma enlargement >33% or >6 mL at 24 hours. Early neurological deterioration as well as mortality and poor long-term outcome (modified Rankin Scale score >2) at 3 months were recorded.

Results—Although LDL-C levels were not correlated with ICH volume (r = -0.18; P = 0.078) or National Institutes of Health Stroke Scale score (r = -0.17; P = 0.091) at baseline, lower LDL-C levels were associated with HG (98.1 ± 33.7 mg/dL versus 117.3 ± 25.8 mg/dL; P = 0.003), early neurological deterioration (89.2 ± 31.8 mg/dL versus 112.4 ± 29.8 mg/dL; P = 0.012), and 3-month mortality (94.9 ± 37.4 mg/dL versus 112.5 ± 28.5 mg/dL; P = 0.029), but not with poor long-term outcome (109.5 ± 31.3 mg/dL versus 108.3 ± 30.5 mg/dL; P = 0.875). Moreover, LDL-C levels were inversely related to the amount of hematoma enlargement at 24 hours (r = -0.31; P = 0.004). In multivariate logistic regression analysis, LDL-C level <95 mg/dL emerged as an independent predictor of HG (OR, 4.24; 95% CI, 1.26–14.24; P = 0.020), early neurological deterioration (OR, 8.27; 95% CI, 1.66–41.16; P = 0.010), and 3-month mortality (OR, 6.34; 95% CI, 1.29–31.3; P = 0.023).

Conclusions—Lower serum LDL-C independently predicts HG, early neurological deterioration, and 3-month mortality after acute ICH. (Stroke. 2011;42:2447-2452.)

Key Words: intracerebral hemorrhage ■ cholesterol ■ low-density lipoprotein cholesterol ■ growth ■ outcome

Intracerebral hemorrhage (ICH) accounts for about 10% of strokes and is associated with poor outcome and high mortality rates.1 Despite its devastating effects and social burden, no proven treatment has been consistently demonstrated to be effective in ameliorating ICH consequences.2 Hematoma growth (HG) has been shown to be an independent determinant of death and disability after ICH,3 and limiting HG represents the main target for emergent therapies for ICH.2 HG occurs mainly during the first hours after ICH onset, most frequently within the first 6 hours.4–6 Besides earlier time to computed tomography (CT) scan, several factors have been related to HG, including larger baseline ICH volume, irregularly shaped hematoma, liver disease, alcohol consumption, higher systolic blood pressure, hyperglycemia, and hypofibrinogenemia.6–8 A post hoc analysis of the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial showed that lower serum total cholesterol (total-C) levels were related to HG.8 Decreased low-density lipoprotein cholesterol (LDL-C)9 and total-C10–12 levels have been previously demonstrated to be associated with a higher risk of ICH. Moreover, both lower total-C and LDL-C levels have been shown to increase risk of death after ICH in several studies.11,13–15 Although lower cholesterol levels have been involved in the destruction of smooth muscle cells in arterial media promoting active
bleeding, the link between LDL-C levels, HG, and clinical deterioration in patients with acute ICH remains largely unknown.

The aim of the present study was to investigate the relationship between LDL-C levels and HG in patients with acute ICH and their impact on clinical outcome.

Subjects and Methods

Study Population
We prospectively evaluated consecutive patients with acute primary supratentorial ICH admitted to our emergency room within 6 hours from symptoms onset. A total of 142 patients were initially evaluated between April 2009 and June 2010. We excluded those patients who were under anticoagulant treatment (n=15), those with a Glasgow Coma Scale (GCS) score <8 (n=17), and those who underwent a surgical procedure (n=2). Finally, 108 patients were included in this study. The ethics committee approved all aspects of the study protocol.

CT Scan Protocol
All patients underwent 2 cranial CT scans: an initial CT scan on admission (<6 hours), and at 24 hours from symptoms onset (follow-up CT scan). All CT scans were performed according to the Neuroradiology Department protocol, with an image matrix of 340×340, 1.5-mm-slice thickness.

ICH location (lobar or deep) and presence of intraventricular extension were recorded on initial CT scan. Hematoma volumes were calculated by 2 neuroradiologists blinded for clinical data on initial and follow-up CT scans using the formula ABC/2. Most previous studies have used the threshold of 33% as the criterion for determining significant HG. However, following the results of the study of Mayer et al, which showed significantly worse outcomes in patients who did not receive recombinant factor VIIa with an absolute mean increase of only 5.8 mL in the group treated with the highest dose, recent works have also used the threshold of 6 mL. Accordingly, we defined significant HG as hematoma enlargement >33% or >6 mL at 24 hours.

Clinical Assessment
On admission, body temperature, systolic and diastolic blood pressure, GCS score, and National Institute of Health Stroke Scale (NIHSS) score were obtained from all patients. GCS score, NIHSS score, and ICH volume at baseline were used as markers of ICH severity.

Early neurological deterioration (END) was defined as an increase of ≥4 points in NIHSS score or death at 24 hours from symptoms onset. Long-term outcome was assessed by means of the modified Rankin Scale (mRS) score at 3 months. We defined poor long-term outcome as mRS score ≥2. In patients with a baseline mRS score >2, we considered it poor long-term outcome when mRS score increased at least 1 point at 3 months.

Laboratory Parameters
The following routine laboratory tests were performed on admission: serum glucose, creatinine, hemoglobin, leucocyte count, platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen.

Serum albumin, total-C, LDL-C, high-density lipoprotein cholesterol, and triglyceride levels were determined in blood samples obtained within the first 24 hours from symptom onset, after a minimum of 12 hours fasting. LDL-C levels were calculated by Friedewald’s formula. When triglyceride levels were >300 mg/dL, LDL-C levels were measured by ultracentrifugation method.

Statistical Analysis
Descriptive and frequency statistical analysis were obtained and comparisons were made by use of the SPSS 17.0 (SPSS, Inc.). Statistical significance for intergroup differences was assessed by Pearson’s χ² or Fisher’s exact test for categorical variables, and by Student t test or Mann-Whitney U test for continuous variables. Correlations between continuous variables were assessed by Spearman’s correlation coefficient. Receiver operating characteristic curves were configured to establish different cut-off points of each continuous variable that optimally predicted HG, END, 3-month mortality, and poor long-term outcome. Multivariate logistic regression analyses were performed to determine factors that could be considered independent predictors of HG and clinical outcome, adjusted by statin pretreatment, serum albumin level, and other possible confounding variables according to univariate analysis results. Variables showing P<0.1 in univariate analysis were included in the multivariate model. A probability value of <0.05 was considered significant for all tests.

Results
The main baseline characteristics are summarized in Table 1. Mean time from symptom onset to initial CT scan was 169.2±84.2 minutes, and mean time to obtain lipid profile sample was 12.1±7.4 hours. Mean LDL-C levels were 109.2±31 mg/dL (102.4±28 mg/dL in statin users, and 110.3±31.4 mg/dL in nonusers), and mean triglyceride levels were 110.5±48.3 mg/dL (maximum value 270).

Of 108 patients, 14 patients did not have a follow-up CT scan (8 of them died <24 hours) and were excluded from HG analysis. HG occurred in 30 patients (31.9%) of 94 who had a follow-up CT scan. In these 94 patients, mean ICH volumes at baseline and at 24 hours were 20.8±21.8 mL and 25.8±29.2 mL, respectively, and mean HG was 5±9.7 mL. From the total sample, 22 patients (20.4%) experienced END. At 3 months, 83 patients (76.9%) had poor long-term outcome, including the 28 patients (25.9%) who died. Median time from onset to death was 3 (1–10) days. Of 28 patients who died within 3 months, 11 patients (39.3%) died within the first 48 hours, 8 patients (28.6%) between 48 hours and day 7, and 9 patients (32.1%) between day 7 and 3 months.

HG was significantly associated with both END (30% of patients who experienced HG deteriorated versus 3.1% of patients without HG; P<0.001), and 3-month mortality (40% of HG patients died versus 6.3% who did not experience HG; P<0.001), but not with poor long-term outcome (86.7% of HG patients had a poor long-term outcome versus 68.8% of no-HG patients; P<0.078).

Relationship Between LDL-C and Hematoma Growth
Potential predictors of HG are shown in Table 1. HG patients had lower LDL-C (Figure) and total-C levels, as well as higher creatinine levels and greater ICH volume at baseline than no-HG patients. LDL-C levels were unrelated to ICH location (lobar 100.6±33.6 mg/dL versus deep 112.6±29.4 mg/dL; P=0.110), and were lower in HG patients in both lobar (86.5±34.5 mg/dL versus 117.4±20.9 mg/dL; P=0.010) and deep (103.9±32.7 mg/dL versus 117.3±27.4 mg/dL; P=0.042) ICH.

Mean time from symptom onset to initial CT scan was 173.6±84.6 minutes in HG patients, and 167.9±83.8 minutes in no-HG patients (P=0.688). Similarly, there were no significant differences in mean time from symptom onset to
obtain lipid profile between HG and no-HG patients (11.9±7.4 hours versus 11.9±7.5 hours; P = 0.956).

Although LDL-C was unrelated to baseline ICH volume (r = −0.18; P = 0.078), LDL-C levels were inversely correlated with the amount of hematoma enlargement at 24 hours (r = −0.31; P = 0.004) and with 24-hour ICH volume (r = −0.23; P = 0.033). A receiver operating characteristic curve identified LDL-C level <95 mg/dL as the value that better predicted HG (sensitivity, 86.9%; specificity, 60%). In contrast, total-C level <168 mg/dL, creatinine level >0.73 mg/dL, and baseline ICH volume >21.9 mL were the cut-off values that better discriminate between presence or absence of HG. In multivariate logistic regression analysis, LDL-C level <95 mg/dL (OR, 4.24; 95% CI, 1.26–14.24; P = 0.020) and baseline ICH volume >21.9 mL (OR, 4.25; 95% CI, 1.14–15.9; P = 0.032) emerged as independent predictors of HG. Using 25th-percentile cut-off points, low LDL-C level (<91 mg/dL; 25th percentile) remained a predictor of HG (OR, 9.17; 95% CI, 3.03–27.69; P < 0.001).

### Relationship Between LDL-C and Clinical Outcome

LDL-C levels were not correlated with markers of ICH severity at baseline including ICH volume (r = −0.18; P = 0.078), GCS score (r = 0.12; P = 0.255), and NIHSS score (r = −0.17; P = 0.091). Similarly, patients pretreated with statins had similar

### Figure

Relationship between low-density lipoprotein cholesterol (LDL-C) levels and hematoma growth (HG), early neurological deterioration (END), 3-month mortality, and poor long-term outcome (mRS >2).
ICH volume (31.5±50.8 mL versus 26.7±29.1 mL; P=0.585), GCS score (15 [11–15] versus 15 [11–15]; P=0.931), and NIHSS score (16 [7–19] versus 17 [11–20]; P=0.548) at baseline than those without, respectively.

END patients had lower GCS score and LDL-C level (Figure); higher NIHSS score, glucose level, and baseline ICH volume; and more frequently had lobar location or intraventricular extension. Table 1 shows factors associated with END. Of these variables, LDL-C level <95 mg/dL (OR, 8.27; 95% CI, 1.66–41.16; P=0.010), ICH volume >21.9 mL (OR, 13.24; 95% CI, 2.52–69.56; P=0.002), and intraventricular extension (OR, 6.94; 95% CI, 1.34–36; P=0.021) emerged as independent predictors of END.

At 3 months, patients with poor long-term outcome or who had died had older age, higher NIHSS score and glucose level, larger baseline ICH volume, and more frequently had intraventricular extension (Table 2). Lower LDL-C level was significantly associated with 3-month mortality, but not with poor long-term outcome (Figure).

Multivariable logistic regression analysis showed that variables independently related to 3-month mortality were LDL-C level <95 mg/dL (OR, 6.34; 95% CI, 1.29–31.3; P=0.023), baseline ICH volume >26 mL (OR, 21.48; 95% CI, 3.85–119.9; P<0.001), intraventricular extension (OR, 7.29; 95% CI, 1.45–36.64; P=0.016), and age >75 years (OR, 16.31; 95% CI, 2.36–112.61; P=0.005). Similarly, LDL-C levels below 25th percentile also predicted END (OR, 4.49; 95% CI, 1.01–20.05; P=0.049) and 3-month mortality (OR, 7.13; 95% CI, 1.33–38.19; P=0.022). Regarding long-term outcome, age >67 years (OR, 3.28; 95% CI, 1.07–9.99; P=0.037), baseline ICH volume >14.2 mL (OR, 6.91; 95% CI, 1.99–23.95; P=0.002), and intraventricular extension (OR, 4.61; 95% CI, 1.29–16.49; P=0.019) independently predicted poor long-term outcome.

When analyzing separately patients with 3-month mRS score 3 to 5 (n=55), LDL-C levels were comparable with those with mRS score ≥2 (n=25; 114.4±27.7 mg/dL versus 108.3±30.5 mg/dL; P=0.388). Variables significantly associated with 3-month mRS score 3 to 5 were higher baseline NIHSS score (16 [11–19] versus 9 [6–16]; P=0.014), higher glucose level (150.2±66.3 mg/dL versus 114±40.4 mg/dL; P=0.049), and intraventricular extension (41.8% versus 16%; P=0.023). After multivariate regression analysis, baseline NIHSS score >14 (OR, 3.7; 95% CI, 1.31–10.47; P=0.013)
and intraventricular extension (OR, 3.64; 95% CI, 1.06–12.54; $P=0.041$) remained as independent predictors of 3-month mRS score 3 to 5.

Finally, regarding ICH location, LDL-C levels were lower in patients with END or who had died at 3 months, respectively, in both lobar (85±34.6 mg/dL versus 108±31.2 mg/dL; $P=0.039$; 84.3±31.2 mg/dL versus 108.7±32.6 mg/dL; $P=0.045$) and deep (98.8±25.7 mg/dL versus 113.6±29.8 mg/dL; $P=0.026$; 105.6±41.8 mg/dL versus 113.8±27.6 mg/dL; $P=0.054$) hematomas. In addition, LDL-C levels were similar in patients with poor long-term outcome than those without in both lobar (95±36.3 mg/dL versus 101.8±33.8 mg/dL; $P=0.690$) and deep (113±30.2 mg/dL versus 111.8±28.9 mg/dL, $P=0.882$) ICH.

**Discussion**

This study shows an association between serum LDL-C levels and risk of HG after an acute supratentorial ICH. LDL-C levels were inversely correlated and independently associated with HG at 24 hours. Moreover, lower LDL-C levels independently predicted END and 3-month mortality. However, in our series, LDL-C was unrelated to poor long-term outcome after acute ICH.

Previous studies focused on the relationship between serum cholesterol levels and risk of ICH have shown divergent results,9–12,21 but overall they suggest increasing ICH risk as LDL-C$^9$ and total-C$^{10–12}$ levels decrease. This effect, however, appears to be unrelated to statin pretreatment in patients without previous stroke.22,23 In our study, an LDL-C level <95 mg/dL emerged as a powerful predictor of HG, END, and 3-month mortality. Although lower total-C levels have previously been reported to be related to HG$^9$ and lower LDL-C levels to 3-month mortality,14,15 to our knowledge, this is the first report on the relationship between LDL-C, HG, and END in patients with acute ICH.

Several factors may influence the relationship between LDL-C, HG, and clinical outcome. Although LDL-C might represent a marker of ICH severity rather than a predictor of HG or clinical outcome, in our series, LDL-C levels were unrelated to baseline ICH volume, GCS, and NIHSS scores. Moreover, LDL-C was inversely correlated with ICH volume at 24 hours, further supporting the relationship between LDL-C and HG. Conversely, statin pretreatment may potentially alter LDL-C levels. However, in our study, no relationship was found between statin pretreatment and HG or clinical outcome.

The mechanisms that explain the association of LDL-C and ICH are unclear. A possible explanation for this relationship would be the role of serum cholesterol levels for maintaining the integrity of vascular vessels. Lower cholesterol levels have been related to the development of medial smooth muscle cell necrosis,16 thus decreasing the resistance to rupture of vascular wall. Moreover, cholesterol levels modify platelet aggregability by their action on the platelet activating factor, so that lower cholesterol levels may decrease platelet aggregation,24,25 thus predisposing to ICH growth.

This study has some limitations. Patients who were under anticoagulant treatment, those comatose, or who underwent a surgical procedure were excluded, which may underrepresent the rate of END and poor outcome in our series. However, patients with these conditions usually receive different treatments than do those without, making difficult any comparison between them. In contrast, both HG and LDL-C were unrelated to poor long-term outcome, which may be explained in part by the relative small sample size and exclusion of patients who died before follow-up CT scan. Similarly, although no influence of LDL-C was found according to ICH location, it may be also explained in part by the relative small sample size. Therefore, larger studies are needed to elucidate the impact of LDL-C level depending on ICH location and on long-term outcome.

In conclusion, in patients with acute primary supratentorial ICH, low LDL-C level (<95 mg/dL) is an independent predictor of HG, END, and mortality at 3 months. However, LDL-C appeared unrelated to long-term outcome.

**Disclosures**

None.

**References**


Serum Low-Density Lipoprotein Cholesterol Level Predicts Hematoma Growth and Clinical Outcome After Acute Intracerebral Hemorrhage

David Rodriguez-Luna, Marta Rubiera, Marc Ribo, Pilar Coscojuela, Jorge Pagola, Socorro Piñeiro, Bernardo Ibarra, Pilar Meler, Olga Maisterra, Francisco Romero, José Álvarez-Sabin and Carlos A. Molina

*Stroke.* 2011;42:2447-2452; originally published online July 28, 2011;
doi: 10.1161/STROKEAHA.110.609461

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 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/42/9/2447

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/10/08/STROKEAHA.110.609461.DC1

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/
Abstract 14

Serum Low-Density Lipoprotein Cholesterol Level Predicts Hematoma Growth and Clinical Outcome After Acute Intracerebral Hemorrhage

David Rodriguez-Luna, MD; Marta Rubiera, MD, PhD; Marc Ribo, MD, PhD; Pilar Coscojuela, MD; Jorge Pagola, MD, PhD; Socorro Piñeiro, MD; Bernardo Ibarra, MD; Pilar Meler, RN; Olga Maisterra, MD; Francisco Romero, MD, PhD; Jose Alvarez-Sabin, MD, PhD; Carlos A. Molina, MD, PhD

(Stroke. 2011;42:2447-2452.)

Key Words: intracerebral hemorrhage ■ cholesterol ■ low-density lipoprotein cholesterol ■ growth ■ outcome

배경과 목적 낮은 혈청 저밀도지질단백질 콜레스테롤(low-density lipoprotein cholesterol, LDL-C) 수치는 뇌내출혈(intracerebral hemorrhage, ICH) 이후의 사망 위험의 증가와 연관되어 있다고 알려져 있다. 그러나 LDL-C 수치와 혈종 증가(hematoma growth, HG)의 연관성은 알려져 있지 않다. 그러므로 저자들은 급성 ICH 환자들에서 LDL-C 수치, HG 및 임상적 결과들 의 관계에 대하여 조사하였다.

방법 저자들은 전향적으로 증상 발생 6시간 이내 전략위(supratentorial) ICH로 진단된 108명의 환자들을 대상으로 연구를 진행하였다. NIHSS (National Institutes of Health Stroke Scale) 점수와 컴퓨터단층촬영에서의 ICH 농도는 내원 시와 24시간 경과 시점에서 조사되었다. 저혈압은 저혈압 24시간 동안 시행되었다. 유의한 HG는 33% 이상 혈종이 증가하거나 24시간째 최초보다 6 mL 넘게 농도가 증가한 경우로 정의되었다. 초기 신경학적 악화, 사망률 및 3개월째 불량한 장기 예후(modified Rankin Scale, mRS) 점수 2초과)를 분석하였다.

결과 LDL-C 수치는 ICH 농도(r=-0,18; P=0,078) 혹은 NIHSS (r=-0,17; P=0,091) 점수와 연관성이 없었으나, 낮은 LDL-C 수치는 HG (98,1±33,7 mg/dL vs. 117,3±25,8 mg/dL; P=0,003), 초기 신경학적 악화(89,2±31,8 mg/dL vs. 112,4 ±29,8 mg/dL; P=0,012) 및 3개월 사망률(94,9±37,4 mg/dL vs. 112,5±28,5 mg/dL; P=0,029)의 통계적 유의성 있는 것으로 나타났으나, 장기 예후(109,5±31,3 mg/dL vs. 108,3±30,5 mg/dL; P=0,875)와는 관련성이 없었다. 또한 LDL-C 수치는 초기 24시간에 혈종 확대량과 음의 상관관계가 있었다(r=-0,31; P=0,004). 다변량 로지스틱 회귀분석에서, LDL-C 수치가 95 mg/dL 미만인 경우에 HG (OR, 4,24; 95% CI, 1,26~14,24; P=0,020), 초기 신경학적 악화(OR, 8,27; 95% CI, 1,66~41,16; P=0,010), 3개월 사망률(OR, 6,34; 95% CI, 1,29~31,3; P=0,023)의 독립적인 예측인자였다.

결론 낮은 혈청 LDL-C 수치는 급성 ICH 이후 독립적으로 HG, 초기 신경학적 악화 및 3개월 사망률을 예측할 수 있는 인자이다.