Low-density lipoprotein level on admission is not associated with postintravenous thrombolysis intracranial hemorrhage in patients with acute ischemic stroke

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ABSTRACT

Intravenous thrombolysis with the tissue plasminogen activator (tPA) is the gold standard for acute ischemic stroke. However, its application is limited because of the concern of the post-tPA intracranial hemorrhage (ICH). Low low-density lipoprotein (LDL) has been speculated to increase the risk of hemorrhagic transformation after ischemic stroke. However, whether LDL is associated with post-tPA ICH remains controversial. The present study obtained the medical records from Shuang Ho Hospital and retrospectively reviewed for the period between August 2009 and December 2016 to investigate the association between LDL and the risk of post-tPA ICH. The differences were analyzed using the Student's t-test, Fisher's exact test, the univariate and stepwise multiple regression model, and $p<0.05$ was considered statistically significant. Among 218 patients, post-tPA ICH was noted in 23 (10.5%) patients. Patients with post-tPA ICH tended to have a lower LDL level (ICH group: 102.00±24.56, non-ICH group: 117.02±37.60 mg/dL, p=0.063). However, after adjustment for the factors might affect the risk of post-tPA ICH, such as stroke severity, onset-to-treatment time interval, and atrial fibrillation (AF), LDL level was not associated with post-tPA ICH whereas AF was the only significant factor increased the risk of post-tPA ICH (adjusted OR: 1.177, 95% CI 1.080 to 1.283). In addition, patients with AF had significant lower LDL level and for patients without AF, LDL was not associated with the post-tPA ICH. In conclusion, LDL level is not associated with the risk of post-tPA ICH in Taiwanese patients with stroke.

Significance of this study

What is already known about this subject?
- The treatment of acute ischemic stroke by tissue plasminogen activator (tPA) causes about 6% of intracranial hemorrhage (ICH).
- Low level of low-density lipoprotein (LDL) is associated with higher risk of hemorrhagic transformation after ischemic stroke.
- Asians are more likely to develop post-tPA ICH.

What are the new findings?
- In Taiwan, patients with post-tPA ICH tended to have a lower LDL level.
- Normolipidemic patients (LDL<130 mg/dL) did not have an increased risk of post-tPA ICH.
- AF was the only significant factor associated with post-tPA ICH.
- LDL level was not associated with post-tPA ICH after excluding the effect of AF.

How might these results change the focus of research or clinical practice?
- Previous concerns about the association between low LDL with post-tPA ICH may be biased by AF.
- Clinicians do not need to worry about 'too low' LDL about the risk of post-tPA ICH.

INTRODUCTION

Currently, the most effective and easily accessible treatment for acute ischemic stroke is intravenous thrombolysis with a recombinant tissue plasminogen activator (tPA), which must be applied within the treatment time window.[1–3] However, post-tPA intracranial hemorrhage (ICH), which may prolong hospital stay and increase mortality, is the major concern of tPA. The risk factors for post-tPA ICH include atrial fibrillation (AF), old age, severe stroke, and recanalization using tPA.[4]

The association between low-density lipoprotein (LDL) and hemorrhagic transformation (HT) after ischemic stroke had been investigated in recent decade. A lower serum lipid level is associated with a higher risk of HT in patients with ischemic stroke.[5–9] It was postulated that low lipid level would damage the integrity of the small cerebral vessels, which increases the risk of HT.[10] Post-tPA ICH is mainly due to HT in the infarct area. However, whether LDL is associated with the risk of post-tPA ICH remains controversial.[11–17] Moreover, the Asian population is more prone to post-tPA ICH[18–20]; nevertheless, relevant information on the association

between lipid profile and post-tPA ICH in the Asian population is lacking.

The present study evaluated the association between LDL and post-tPA ICH by using the data from a single university-affiliated hospital in Taiwan. Our results may provide more evidence for this controversial issue, particularly for the Asian population.

METHODS

Patient selection

Medical records from the stroke registry of Shuang Ho Hospital were retrospectively reviewed for the period between August 2009 and December 2016. During this period, a total of 218 patients with ischemic stroke received intravenous tPA, and their fasting LDL levels were measured within 72 hours after tPA. tPA was mainly performed following the updated American Heart Association/American Stroke Association guidelines. In general, all patients received non-contrast head CT before tPA, and they were intensively monitored for 24 hours after tPA. Additionally, head CT with CT angiography or brain MRI with MR angiography was performed within 72 hours after tPA.

The following data were collected from the medical records: age; sex; history of hypertension, diabetes mellitus, AF, and stroke; onset-to-treatment time; and post-tPA ICH, which was defined according to the criteria of the European Cooperative Acute Stroke Study II.[21] The primary outcome was the overall post-tPA ICH rate. All CT/MR results were analyzed by two independent neurologists.

Statistical analyses

All statistical analyses were performed using SPSS for Windows V.10 (V.19; SPSS). Continuous variables are presented as mean±SD, and categorical variables are expressed as percentages with corresponding 95% confidential intervals (CIs). The differences were analyzed using the Student's t-test and Fisher's exact test. The univariate logistic regression model was applied to assess the crude odds ratio (OR) of post-tPA ICH affected by AF, LDL, National Institutes of Health Stroke Scale (NIHSS) and onset-to-treatment time interval. The stepwise multiple logistic regression model applied to obtain the adjusted OR using a probability of 0.05 as the entry value and 0.10 as the removal value. A p value of <0.05 was considered statistically significant.

RESULTS

Overall, 218 patients with acute ischemic stroke received intravenous tPA treatment. Their mean age was 68.74±11.60 years old, and 92 (42.2%) of them were women. Their average onset-to-treatment time was 118.16±40.86 minutes, and their mean NIHSS score was 13.05±6.54. Follow-up neuroimages revealed overall post-tPA ICH in 23 (10.5%) patients. In comparison with patients without post-tPA ICH, those with ICH were more likely to have AF (65.2% vs 32.8% for patients with/without post-tPA ICH, p=0.001) and greater stroke severity (15.83±5.84 vs 12.72±6.56 for patients with/without post-tPA ICH in NIHSS, p=0.031). In addition, patients with post-tPA ICH tended to have slightly lower LDL (102.00±24.56 vs 117.02±37.60 mg/dL for patients with/without post-tPA ICH, p=0.063), and less likely to have hyperlipidemia (fasting LDL≥130 mg/dL) (13.0% vs 30.3% for patients with/without post-tPA ICH, p=0.093) (table 1).

Table 1 Comparison of the demographic data between patients with and without post-tPA hemorrhage

	Post-tPA ICH (–) n=195	Post-tPA ICH (+) n=23	p Values
Age (y)	68.59±11.95	69.96±8.22	0.482
Female (%)	84 (43.1)	8 (34.8)	0.509
Hypertension (%)	155 (79.5)	19 (82.6)	0.764
Diabetes (%)	60 (30.8)	7 (30.4)	1.000
AF (%)	54 (32.8)	15 (65.2)	0.001
OTT (min)	119.40±42.09	107.65±26.91	0.073
NIHSS	12.72±6.56	15.83±5.84	0.031
LDL (mg/dL)	117.02±37.60	102.00±24.56	0.063
LDL≥130 mg/dL (%)	59 (30.3)	3 (13.0)	0.093

Data are presented as mean±SD or number (percentage).
AF, atrial fibrillation; ICH, intracranial hemorrhage; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; tPA, recombinant tissue plasminogen activator.

Considering that several factors, such as AF, stroke severity, onset-to-treatment time interval and LDL demonstrated in table 1, were significantly or trendily (p<0.1) different between hemorrhage/non-hemorrhage groups, we conduct the regression models to investigate their impact on post-tPA ICH. In univariate regression model, the presence of AF and higher stroke severity were significantly associated with increased risk of post-tPA ICH (table 2). Neither LDL nor onset-to-treatment time interval affects the risk of post-tPA ICH. Further analysis through stepwise regression model found that AF was the only significant factor associated with increased risk of post-tPA ICH (adjusted OR: 1.177, 95% CI 1.080 to 1.283), but not the rest of the factors (table 2). In addition, patients with AF had significant lower LDL level compared with non-AF patients (103.48±28.48 vs 120.96±38.78 mg/dL for patients with/without AF, p<0.001).

Lastly, we analyzed the association between LDL and post-tPA ICH solely on patients without AF. There was neither significant difference on the fasting LDL level between non-AF patients with and without post-tPA ICH (104.00±33.38 vs 121.92±38.94 mg/dL for patients with/without post-tPA ICH, p=0.205) nor the likelihood of hyperlipidemia (LDL≥130 mg/dL) (25.0% vs 33.3% for patients with/without post-tPA ICH, p=1.000) (table 3).

Table 2 Regression model of the risk of post-tPA ICH related to different conditions

	Crude OR	95% CI	Adjusted OR	95% CI
AF	1.180	1.087 to 1.281	1.177	1.080 to 1.283
LDL (mg/dL)	0.999	0.998 to 1.000	–	–
OTT (min)	0.999	0.998 to 1.000	–	–
NIHSS (points)	1.007	1.001 to 1.013	–	–

AF, atrial fibrillation; ICH, intracranial hemorrhage; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; tPA, recombinant tissue plasminogen activator.

Table 3 Comparison of the level of LDL and number of hyperlipidemia (LDL≥130 mg/dL) between non-AF patients with and without post-tPA hemorrhage

	Post-tPA ICH (–) n=141	Post-tPA ICH (+) n=8	p Values
LDL (mg/dL)	121.92±38.94	104.00±33.38	0.205
LDL≥130 mg/dL (%)	47 (33.3)	2 (25. 0)	1.000

Data are presented as Pearson correlation coefficient (p value).
AF, atrial fibrillation; ICH, intracranial hemorrhage; LDL, low-density lipoprotein; tPA, recombinant tissue plasminogen activator.

DISCUSSION

The present study addressed the controversial issue of whether low LDL increases the risk of post-tPA ICH. This study demonstrated that although LDL tended to be negatively associated with post-tPA ICH, this correlation was possibly confounded by AF. AF was significantly associated with post-tPA ICH and patients with AF had significant lower LDL. Excluding the effect of AF, no association was observed between LDL and post-tPA ICH. The present study is the first to report that the association between LDL and post-tPA ICH is misled due to AF.

Currently, whether LDL is associated with postischemic stroke ICH remains controversial. Cholesterol is one of the most important components for maintaining membrane integrity and for providing resistance to the rupture of small vessels.[22] HT is defined as ICH occurrence after ischemic stroke; in patients with HT, blood extravasation is observed around small vessels because of the breakdown of the blood–brain barrier,[23 24] and plasma accumulation and edematous of brain parenchyma are also observed, which are associated with the deterioration of the neurological status of the patients. Based on the association between cholesterol and membrane integrity, some studies have proven the positive association of low LDL with a high risk of ICH.[12 15] However, Kim *et al* showed that the incidence of ICH increased only in the cardioembolic group, regardless of the LDL level.[5] HT is one of the most well-known characteristics of cardioembolic stroke; it results from spontaneous recanalization and reperfusion injury in the brain, which induce endothelial cell damage and subsequent extravasation. Thrombolysis enhances the possibility of recanalization and mitigates subsequent reperfusion injury-related damage, which can lead to post-tPA ICH.

Large artery stenosis, cardioembolism, and small vessel occlusion are the main causes of ischemic stroke, and AF is the major etiology of cardioembolism.[25] The fundamental pathogenesis of large artery stenosis and small vessel occlusion is atherosclerosis.[26 27] By contrast, AF may result from ischemic heart disease, structural heart disease, autonomic dysfunction, or hyperthyroidism,[28] which may not be associated with atherosclerosis. Because LDL plays an essential role in atherosclerosis,[29–31] the observation of a significantly higher mean LDL level in non-AF stroke patients is not surprising. In addition, AF is strongly associated with post-tPA ICH due to the aforementioned recanalization and reperfusion injury.[32–34] This indirect connection may explain why LDL was lower in patients with post-tPA ICH and why the correlation was not observed after adjustment for AF.

The present study has some limitations. First, statins are the mainstream treatment for lowering LDL and are associated with ICH. The present study did not investigate the effect of statins on post-tPA ICH due to incomplete medical records. Because Shuang Ho Hospital has been in operation since August 2009, half of the study patients were new to the hospital, and their prescription history was unclear. The other limitation is the timing of blood sampling for measuring fasting LDL. It was performed within 72 hours after tPA under the overnight fasting condition. However, fasting for the following 24 hours is routine clinical practice for patients receiving tPA; therefore, the LDL level afterwards may not be in line with the LDL level during tPA.[35 36]

In summary, the present study revealed that LDL was indirectly associated with post-tPA ICH, and the association was confounded by AF. After adjustment for the confounding effect of AF, LDL was not associated with post-tPA ICH. These findings ease the issue about lowering LDL and post-tPA ICH. For patients with abnormal elevated LDL and a high risk of ischemic stroke, clinicians need not be concerned about the risk of post-tPA ICH before prescribing a lipid-lowering agent.

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REFERENCES

1 Demaerschalk BM, Kleindorfer DO, Adeoye OM, *et al*. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. *Stroke* 2016;47:581–641.
2 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–8.
3 Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–29.
4 Saver JL. Hemorrhage after thrombolytic therapy for stroke: the clinically relevant number needed to harm. *Stroke* 2007;38:2279–83.
5 Kim BJ, Lee S-H, Ryu W-S, *et al*. Low level of low-density lipoprotein cholesterol increases hemorrhagic transformation in large artery atherothrombosis but not in cardioembolism. *Stroke* 2009;40:1627–32.
6 Paciaroni M, Agnelli G, Corea F, *et al*. Low levels of low-density lipoprotein cholesterol increase hemorrhagic transformation but not parenchimal hematoma in large artery atherothrombosisis. *Stroke* 2009;40:e544.
7 Nardi K, Leys D, Eusebi P, *et al*. Influence of lipid profiles on the risk of hemorrhagic transformation after ischemic stroke: systematic review. *Cerebrovasc Dis Extra* 2011;1:130–41.
8 D'Amelio M, Terruso V, Famoso G, *et al*. Cholesterol levels and risk of hemorrhagic transformation after acute ischemic stroke. *Cerebrovasc Dis* 2011;32:234–8.
9 Yang N, Lin M, Wang BG, *et al*. Low level of low-density lipoprotein cholesterol is related with increased hemorrhagic transformation after acute ischemic cerebral infarction. *Eur Rev Med Pharmacol Sci* 2016;20:673–8.
10 Reed DM. The paradox of high risk of stroke in populations with low risk of coronary heart disease. *Am J Epidemiol* 1990;131:579–88.
11 Messé SR, Pervez MA, Smith EE, *et al*. Lipid profile, lipid-lowering medications, and intracerebral hemorrhage after tPA in get with the guidelines-stroke. *Stroke* 2013;44:1354–9.

12 Bang OY, Saver JL, Liebeskind DS, *et al*. Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. *Neurology* 2007;68:737–42.
13 Engelter ST, Soinne L, Ringleb P, *et al*. IV thrombolysis and statins. *Neurology* 2011;77:888–95.
14 Meseguer E, Mazighi M, Lapergue B, *et al*. Outcomes after thrombolysis in AIS according to prior statin use: a registry and review. *Neurology* 2012;79:1817–23.
15 Nardi K, Engelter S, Strbian D, *et al*. Lipid profiles and outcome in patients treated by intravenous thrombolysis for cerebral ischemia. *Neurology* 2012;79:1101–8.
16 Uyttenboogaart M, Koch MW, Koopman K, *et al*. Lipid profile, statin use, and outcome after intravenous thrombolysis for acute ischaemic stroke. *J Neurol* 2008;255:875–80.
17 Rocco A, Sykora M, Ringleb P, *et al*. Impact of statin use and lipid profile on symptomatic intracerebral haemorrhage, outcome and mortality after intravenous thrombolysis in acute stroke. *Cerebrovasc Dis* 2012;33:362–8.
18 Chao AC, Hsu HY, Chung CP, *et al*. Outcomes of thrombolytic therapy for acute ischemic stroke in Chinese patients: the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study. *Stroke* 2010;41:885–90.
19 Dharmasaroja PA, Muengtaweepongsa S, Dharmasaroja P. Intravenous thrombolysis in Thai patients with acute ischemic stroke: role of aging. *J Stroke Cerebrovasc Dis* 2013;22:227–31.
20 Mehta RH, Cox M, Smith EE, *et al*. Race/Ethnic differences in the risk of hemorrhagic complications among patients with ischemic stroke receiving thrombolytic therapy. *Stroke* 2014;45:2263–9.
21 Jenkinson D, Ford G, Freemantle N. ECASS-II: intravenous alteplase in acute ischaemic stroke. European Co-operative Acute Stroke Study-II. *Lancet* 1999;353:67–8.
22 Kim BJ, Lee SH, Ryu WS, *et al*. Low level of low-density lipoprotein cholesterol increases hemorrhagic transformation in large artery atherothrombosis but not in cardioembolism. *Stroke* 2009;40:1627–32.
23 Lee SH, Bae HJ, Yoon BW, *et al*. Low concentration of serum total cholesterol is associated with multifocal signal loss lesions on gradient-echo magnetic resonance imaging: analysis of risk factors for multifocal signal loss lesions. *Stroke* 2002;33:2845–9.
24 Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *J Neuropathol Exp Neurol* 1971;30:536–50.
25 Krafft PR, Bailey EL, Lekic T, *et al*. Etiology of stroke and choice of models. *Int J Stroke* 2012;7:398–406.
26 Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. *Lancet Neurol* 2013;12:1106–14.
27 Xu WH, Wh X. Large artery: an important target for cerebral small vessel diseases. *Ann Transl Med* 2014;2:78.
28 Markides V, Schilling RJ. Atrial fibrillation: classification, pathophysiology, mechanisms and drug treatment. *Heart* 2003;89:939–43.
29 Mitra S, Deshmukh A, Sachdeva R, *et al*. Oxidized low-density lipoprotein and atherosclerosis implications in antioxidant therapy. *Am J Med Sci* 2011;342:135–42.
30 Badimon L, Vilahur G. LDL-cholesterol versus HDL-cholesterol in the atherosclerotic plaque: inflammatory resolution versus thrombotic chaos. *Ann N Y Acad Sci* 2012;1254:18–32.
31 Steinberg D, Witztum JL. Oxidized low-density lipoprotein and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2010;30:2311–6.
32 Zhao Q, Li X, Dong W, *et al*. Factors associated with thrombolysis outcome in ischemic stroke patients with atrial fibrillation. *Neurosci Bull* 2016;32:145–52.
33 Saposnik G, Gladstone D, Raptis R, *et al*. Atrial fibrillation in ischemic stroke: predicting response to thrombolysis and clinical outcomes. *Stroke* 2013;44:99–104.
34 Padjen V, Jovanovic D, Berisavac I, *et al*. Effect of intravenous thrombolysis on stroke associated with atrial fibrillation. *J Stroke Cerebrovasc Dis* 2014;23:2199–205.
35 Gruchot M, Graeter T, Oeztuerk S, *et al*. Fasting time and lipid parameters: association with hepatic steatosis--data from a random population sample. *Lipids Health Dis* 2014;13:18.
36 Mora S, Rifai N, Buring JE, *et al*. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. *Circulation* 2008;118:993–1001.