Lipid paradox in statin-naïve acute ischemic stroke

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Background– Low lipid level is associated with better cardiovascular outcome. However, lipid paradox indicating low lipid level has worse outcome can be seen under acute injury in some diseases. The present study was designed to clarify the prognostic significance of acute-phase lipid levels within 1 day after admission for stroke on mortality in first-ever, statin-naïve acute ischemic (IS) and hemorrhagic stroke (HS).

Methods– This observational study was conducted using the data from Stroke Registry In Chang-Gung Healthcare System (SRICHs) between 2009 and 2012. Patients with recurrent stroke, onset of symptoms >1 day and history of lipid-lowering agents prior to index stroke were excluded. Stroke was classified into IS and hypertension-related HS. The primary outcomes were 30-day and 1-year mortality identified by linkage to national death registry for date and cause of death. Receiver operating characteristic curve analysis and multivariate Cox proportional hazard models were used to examine the association of admission lipids with mortality.

Results– Among 18,268 admitted stroke patients, 3,746 IS and 465 HS were eligible for analysis. In IS, total cholesterol (TC) <163.5mg/dL, triglyceride (TG) <94.5mg/dL, low-density lipoprotein (LDL) <100mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) <130.5mg/dL and TC/HDL ratio <4.06 had significantly higher risk for 30-day/1-year mortality with hazard ratio (HR) of 2.05/1.37, 1.65/1.31, 1.68/1.38, 1.80/1.41 and 1.58/1.38, respectively, compared to high TC, TG, LDL, non-HDL-C and TC/HDL ratio (all p<0.01, Table 2). In HS, lipid profiles were not associated with mortality, except HDL for 30-day mortality (p=0.025) and high uric acid concentrations for 30-day and 1-year mortality (p=0.002, 0.012, respectively).

High fasting glucose and high NIHSS score at admission were associated with higher 30-day and 1-year mortality in both IS and HS and low blood pressure only in IS (p<0.05). Synergic effects on mortality were found when low lipids were incorporating with high fasting glucose, low blood pressure and high NIHSS score in IS (p<0.05, Table 1).

Conclusions– Lipid paradox showing low acute-phase lipid levels with high mortality could be seen in statin-naïve acute IS but not HS. The mortality in IS was increased when low lipids were incorporating with high fasting glucose, low blood pressure and high NIHSS score.

Table 1. Hazard ratio of 30-day and 1-year mortality according to lipid levels with NIHSS score, DBP and fasting glucose in first-ever, statin-naïve acute ischemic stroke

	30-day				1-year			
	HR	95% CI		P value	HR	95% CI		P value
		Lower	Upper			Lower	Upper	
Variables at admission in ischemic stroke								
Low TC	2.05	1.47	2.86	<0.001*	1.37	1.13	1.66	0.001*
Low TC & high NIHSS	43.9	22.1	87.4	<0.001*	6.61	4.91	8.88	<0.001*
Low TC & low MBP	3.18	2.10	4.80	0.001*	1.89	1.47	2.44	<0.001*
Low TC & high FG	8.08	4.67	14.0	<0.001*	2.93	2.21	3.87	<0.001*
Low TG	1.65	1.16	2.34	0.005*	1.31	1.08	1.60	0.007*
Low TG & high NIHSS	21.5	11.5	40.3	<0.001*	5.45	4.05	7.33	<0.001*
Low TG & low MBP	2.83	1.76	4.57	<0.001*	1.73	1.31	2.30	<0.001*
Low TG & high FG	6.10	3.45	10.8	<0.001*	2.65	1.98	3.54	<0.001*
Low LDL	1.68	1.21	2.33	0.002	1.38	1.15	1.67	<0.001*
Low LDL & high NIHSS	38.2	19.2	76.3	<0.001*	6.83	5.07	9.21	<0.001*
Low LDL & low MBP	2.74	1.82	4.13	<0.001*	1.92	1.49	2.47	<0.001*
Low LDL & high FG	6.66	3.85	11.5	<0.001*	2.85	2.15	3.78	<0.001*
Low Non-HDL-C	1.80	1.27	2.57	0.001*	1.41	1.16	1.72	0.001*
Low Non-HDL-C & high NIHSS	35.5	17.4	72.5	<0.001*	7.11	5.20	9.72	<0.001*
Low Non-HDL-C & low MBP	2.64	1.72	4.06	<0.001*	1.90	1.45	2.48	<0.001*
Low Non-HDL-C & high FG	6.89	3.80	12.5	<0.001*	2.94	2.19	3.95	<0.001*
Low TC/HDL ratio	1.58	1.13	2.23	0.009*	1.38	1.13	1.67	0.001*
Low TC/HDL ratio & high NIHSS	21.0	11.6	38.1	<0.001*	5.97	4.44	8.02	<0.001*
Low TC/HDL & low MBP	2.52	1.61	3.96	<0.001*	1.87	1.41	2.46	<0.001*
Low TC/HDL & high FG	5.51	3.17	9.58	<0.001*	2.78	2.09	3.69	<0.001*

*p<0.05. DBP= diastolic blood pressure, HR= hazard ratio, CI= confidence interval, NIHSS= national institutes of health stroke scale, TC= total cholesterol, TG= triglyceride, FG= fasting glucose, LDL= Low-density lipoprotein, HDL= High-density lipoprotein, Non-HDL-C= Non-HDL cholesterol, TC/HDL= total cholesterol/HDL ratio, UA= uric acid. Cut-off points of TC, NIHSS, SBP, FG, LDL, Non-HDL-C and TC/HDL= 163.5/163.5 mg/dL, 12.5/10.5, 140/140 mmHg, 108.9/108.9 mg/dL, 100/100 mg/dL, 130.5/130.5 mg/dL and 4.06/4.04 for 30-day/1-year mortality in first-ever ischemic stroke. Multivariate Cox proportional hazard model after adjusting age, sex, age × sex (interaction), atrial fibrillation, smoking, alcohol, hypertension, diabetes mellitus, and family history of stroke for 30-day mortality; age, sex, age × sex (interaction), atrial fibrillation, smoking, alcohol, hypertension, diabetes mellitus, family history of coronary artery disease and family history of stroke for 1-year mortality in first-ever ischemic stroke.

Table 2. Clinical findings and hazard ratio of 30-day and 1-year mortality in first-ever, statin-naïve acute ischemic stroke

Clinical findings and NIHSS	Ischemic stroke- 30-day					Ischemic stroke- 1-year				
	Survival		Mortality	p value	Cut-off point	HR	Survival		Mortality	p value
	n=3,617	n=129					n=3,338	n=408		
Total cholesterol (mg/dL)	179 (154,206)	160 (133,198)	<0.001*	163.5	2.05	1.47	180 (155,207)	166 (136,195)	<0.001*	163.5
Triglyceride (mg/dL)	108 (78,155)	88 (59,117)	<0.001*	94.5	1.65	1.16	110 (79,157)	89 (66,119)	<0.001*	94.5
Low-density lipoprotein (LDL; mg/dL)	111 (90,134)	100 (74,129)	0.004*	100	1.68	1.21	112 (91,135)	101 (79,126)	<0.001*	100
High-density lipoprotein (HDL; mg/dL)	41 (35,50)	43 (33,53)	0.835	39.8	1.37	0.99	41 (35,50)	42 (33,52)	0.914	43.2
Non-HDL cholesterol (mg/dL)	135 (111,162)	116 (91,150)	<0.001*	130.5	1.80	1.27	136 (113,162)	119 (94,149)	<0.001*	130.5
Total cholesterol/HDL ratio	4.3 (3.4,5.2)	3.8 (3.2,5.0)	0.009*	4.06	1.58	1.13	4.3 (3.5,5.2)	3.8 (3.1,4.9)	<0.001*	4.04
Systolic blood pressure (mmHg)	151 (134,170)	147 (128,174)	0.164	140	1.37	0.99	151 (135,170)	148 (130,170)	0.009*	140
Diastolic blood pressure (mmHg)	85 (76,96)	79 (67,95)	<0.001*	79.5	1.82	1.32	86 (77,96)	80 (70,93)	<0.001*	69.5
Mean blood pressure (mmHg)	108 (97,120)	103 (88,119)	0.008*	99.8	1.80	1.31	108 (97,121)	103 (91,117)	<0.001*	99.8
Fasting glucose (mg/dL)	114 (95,152)	148 (113,190)	<0.001*	108.9	3.44	2.41	114 (94,151)	133 (106,181)	<0.001*	108.9
Uric acid (mg/dL)	5.5 (4.5,6.6)	5.4 (4.0,7.0)	0.608	8.0	0.87	0.46	5.5 (4.5,6.6)	5.7 (4.1,7.0)	0.890	8.0
NIHSS score	4.0 (2.0,9.0)	20 (14,29)	<0.001*	12.5	17.1	11.2	4.0 (2.0,8.0)	14 (6.0,22)	<0.001*	10.5

*p<0.05. NIHSS= national institutes of health stroke scale. HR= hazard ratio, CI= confidence interval. Median (Q1,Q3) are reported for continuous variables using Mann-Whitney U test.

Multivariate Cox proportional hazard model for dichotomous data after adjusting age, sex, age × sex (interaction), atrial fibrillation, smoking, alcohol, hypertension, diabetes mellitus, and family history of coronary artery disease for 30-day mortality; age, sex, atrial fibrillation, smoking, alcohol, hypertension, diabetes mellitus, family history of coronary artery disease and family history of stroke for 1-year mortality.

Cut-off points are obtained from receiver operating characteristic curves except LDL, systolic blood pressure and uric acid which are obtained from normal levels according to local guideline.