

Fasting and Non-Fasting Triglycerides in Patients With Acute Ischemic Stroke

Jun Yup Kim

Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine

Keon-Joo Lee

Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine

Jihoon Kang

Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine

Beom Joon Kim

Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine

Moon-Ku Han

Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine

Kyusik Kang

Department of Neurology, Nowon Eulji Medical Center, Eulji University

Min-Surk Kye

Department of Neurology, Uijeonbu Eulji Medical Center, Eulji University

Jong-Moo Park

Department of Neurology, Uijeonbu Eulji Medical Center, Eulji University

Tai Hwan Park

Department of Neurology, Seoul Medical Center

Hong-Kyun Park

Department of Neurology, Inje University Ilsan Paik Hospital

Yong-Jin Cho

Department of Neurology, Inje University Ilsan Paik Hospital

Keun-Sik Hong

Department of Neurology, Inje University Ilsan Paik Hospital

Kyung Bok Lee

Department of Neurology, Soonchunhyang University Hospital, Soonchunhyang University College of Medicine

Myung Suk Jang

Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine

Ji Sung Lee

Clinical Research Center, Asan Institute for Life Sciences, Asan Medical Center

Juneyoung Lee

Department of Biostatistics, Korea University College of Medicine

Hee-Joon Bae (✉ braindoc@snu.ac.kr)

Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine

Research Article

Keywords: Triglycerides, postprandial, fasting triglycerides, non-fasting triglycerides, ischemic stroke

Posted Date: August 6th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-750314/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Journal of Korean Medical Science on January 1st, 2022. See the published version at <https://doi.org/10.3346/jkms.2022.37.e100>.

Abstract

Introduction:

Clinical implications of elevated fasting triglycerides (FTG) and non-fasting triglycerides (NFTG) in acute ischemic stroke (AIS) remain unknown. We aimed to elucidate the correlation and clinical significance of FTG and NFTG levels in AIS patients.

Methods

Using a multicenter prospective stroke registry, we identified AIS patients hospitalized within 24h of onset with available NFTG results. The primary outcome was a composite of stroke recurrence, myocardial infarction, and all-cause mortality up to one year.

Results

This study analyzed 2,176 patients. The prevalence of fasting and non-fasting hypertriglyceridemia was 11.5% and 24.6%, respectively. Multivariate analysis revealed that younger age, diabetes, higher body mass index and initial systolic blood pressure were independently associated with both fasting and non-fasting hypertriglyceridemia (all $p < 0.05$). Patients with higher quartiles of NFTG were more likely to be male, younger, ever-smokers, diabetic, and have family histories of premature coronary heart disease and stroke (all $p < 0.05$). Similar tendencies were observed for FTG. The composite outcome was not associated with FTG or NFTG quartiles.

Conclusion

The fasting and non-fasting hypertriglyceridemia were prevalent in AIS patients and showed similar clinical characteristics and outcomes. High FTG and NFTG levels were not associated with occurrence of subsequent clinical events up to one year.

Introduction

In the general population, the lipid profile is conventionally measured in the blood collected after fasting for at least 8 h.¹ This is because an increase in the triglyceride (TG) level is seen during a fat tolerance test, in which patients typically consume 1 g fat/kg of body weight.^{2,3} However, non-fasting TG (NFTG) has been reported to be associated with the risk of future occurrence of cardiovascular events,⁵ and it could be a better predictor of such events as compared to fasting TG (FTG).^{4,5} Furthermore, because most people eat regularly throughout the day and are strictly fasting only for a few hours in the morning, the NFTG level might be a better physiological indicator of the average TG concentrations in the blood

rather than the FTG level.^{1,6} Therefore, in some countries, such as Denmark, NFTG has been the standard since 2009.¹

Most of the current knowledge about the clinical significance of FTG and NFTG is from previous studies conducted on the general population.^{1,4-6} When discussing the role of FTG and NFTG in patients with acute ischemic stroke (AIS), the important question is whether FTG measurements are essential in the management of AIS. This study aimed to answer this question by (1) describing and comparing the FTG and NFTG concentrations in patients with AIS; (2) comparing their demographics, vascular risk factors, and stroke profiles according to the FTG and NFTG quartiles; (3) exploring the clinical determinants of the elevated FTG and NFTG levels; and (4) analyzing the impact of elevated FTG and NFTG levels on clinical outcomes.

Methods

Study design and population

This study was based on the Clinical Research Collaboration for Stroke-Korea (CRCS-K) registry, a web-based, nationwide, prospective, multicenter stroke registry established in 2008.^{7,8} From the registry database, we identified consecutive patients with AIS, who were admitted to the five participating hospitals within 24 h of symptom onset between October 2009 and November 2014, showing relevant ischemic lesions on diffusion-weighted imaging. The exclusion criteria were unavailability of information regarding the FTG or NFTG levels, unknown last mealtime or blood sampling time of lipid levels, or interval of > 8 h between the last mealtime and first sampling time for the random TG level (i.e., whose lipid profiles were regarded as fasting). Finally, 2,176 patients with AIS were included in this study (Supplemental Fig. 1).

The diagnostic evaluation and management of AIS in the participating centers were performed according to contemporary clinical practice guidelines, institutional protocols, and at the discretion of the treating physicians in charge of patient care.⁹ The collection of clinical information for monitoring and improving the quality of stroke care in the CRCS-K registry was approved by the Institutional Review Boards of the participating centers without patient consent to ensure anonymity of data and minimal risk to participants. We obtained additional approval for the use of the registry database for this study.

Data collection

Data regarding age, sex, body mass index (BMI), laboratory findings (systolic blood pressure [SBP], diastolic blood pressure, and fasting and non-fasting lipid and glucose levels), vascular risk factors (history of stroke and coronary heart disease [CHD], hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and smoking status), family history of stroke and CHD, and stroke characteristics (stroke severity and subtypes) were obtained directly from the CRCS-K registry database.

In all the participating centers, it was recommended to measure lipid concentrations, including total cholesterol, TG, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol at the time of hospitalization without intentional fasting. These were referred to as the non-fasting lipid concentrations, if the blood sampling was performed within 8 h from patients' last mealtime. Most blood samples for the assay of non-fasting lipid concentrations were drawn in the emergency room. Fasting lipid concentrations were measured on the first morning of hospitalization after overnight fasting.

The primary clinical outcome measure of this study was a composite of stroke recurrence, myocardial infarction, and all-cause mortality, captured prospectively up to one year after the index stroke by reviewing medical records and/or conducting structured telephonic interviews by the stroke coordinators of the participating centers. The detailed definitions and protocols for collecting clinical outcomes in the CRCS-K registry have been described elsewhere.^{7,8} The secondary outcome measure was stroke recurrence.

Statistical analyses

Scatter plots and Pearson correlation coefficients were used to depict and compare the distribution of fasting and non-fasting lipid levels. Baseline characteristics of the participants were compared according to FTG and NFTG quartiles using the Pearson's chi-square test for categorical variables and analysis of variance or Kruskal-Wallis tests for continuous variables.

To explore the clinical determinants of the two correlated dependent variables, fasting and non-fasting hypertriglyceridemia (defined as TG \geq 200 mg/dL),¹⁰ we performed multivariate logistic regression analysis with the generalized estimating equation method with respect to the correlational structure between them.¹¹ For each potential determinant, the equality of odds ratios (ORs) between fasting and non-fasting hypertriglyceridemia was examined using the Wald test.

Influences of the FTG and NFTG quartiles on clinical outcomes were evaluated using Cox proportional hazard models. Unadjusted and adjusted hazard ratios with 95% confidence intervals were estimated. Variables for adjustment were predetermined based on previous literature and clinical relevance that included age, sex, history of stroke or transient ischemic attack (TIA), history of CHD, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, ever-smoking, statin use at discharge, antithrombotics at discharge, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification with some modifications¹². A two-sided *p-value* < 0.05 was considered statistically significant. Statistical analysis was performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA) and Statistical Package for the Social Sciences (IBM SPSS version 19.0.1; IBM Corporation, Armonk, NY, USA).

Ethics declarations

Ethical approval for this study was obtained from the Institutional Review Boards of the Seoul National University Bundang Hospital without patient consent to ensure anonymity of data and minimal risk to participants. The Institutional Review Boards of the Seoul National University Bundang Hospital waived the need for patient/care-giver consent.

Results

Among 2,176 eligible patients, the distribution of fasting and non-fasting lipid concentrations was mostly bell-shaped and correlated well with each other (Supplemental Fig. 2 and Fig. 1). The mean (\pm standard deviation) values of fasting and non-fasting lipid concentrations were 171.3 ± 40.8 and 186.3 ± 45.5 mg/dL for total cholesterol, 120.8 ± 80.5 and 160.1 ± 115.3 mg/dL for TG, 43.7 ± 12.2 and 48.7 ± 18.1 mg/dL for HDL cholesterol, and 103.6 ± 34.9 and 108.3 ± 39.0 mg/dL for LDL cholesterol, respectively. Pearson correlation coefficients between fasting and non-fasting lipid concentrations were 0.88 for total cholesterol, 0.70 for TG, 0.60 for HDL cholesterol, and 0.85 for LDL cholesterol ($p < 0.001$ for all). Non-fasting TG concentrations tended to be higher than fasting concentrations up to 4 h after meals (Supplemental Fig. 3). Comparisons of non-fasting lipid concentrations among the quartiles of intervals between the last mealtime and sampling time showed a significant difference only for TG (Supplemental table 1).

When comparing the baseline characteristics according to the NFTG quartiles, patients with higher quartiles were more likely to be male, younger, and have large artery atherosclerosis with an ischemic stroke subtype and traditional vascular risk factors, including family history of premature CHD and stroke (Table 1). Similar tendencies were found in the analysis of the FTG quartiles (Supplemental table 2).

Table 1
Baseline characteristics according to non-fasting triglyceride levels

	< 87 mg/dL (n = 530)	87–130 mg/dL (n = 555)	130–197 mg/dL (n = 544)	≥ 197 mg/dL (n = 547)	p- value
Males, number (%)	304 (57.4)	325 (58.6)	339 (62.3)	381 (69.7)	< 0.001
Age (years)	68.8 ± 13.9	69.0 ± 13.3	66.8 ± 12.2	63.4 ± 12.4	< 0.001
BMI (kg/m ²)	22.8 ± 3.3	23.6 ± 3.7	23.8 ± 3.2	24.8 ± 3.1	0.08
Abdominal circumference (cm)	82.4 ± 9.7	84.7 ± 9.0	85.2 ± 9.8	87.8 ± 9.2	< 0.001
Initial SBP (mmHg)	146.5 ± 26.7	152.6 ± 27.1	152.9 ± 27.8	157.6 ± 29.2	< 0.001
Medical history					
Stroke or TIA, number (%)	134 (25.3)	133 (24.0)	124 (22.8)	93 (17.0)	0.01
CHD, number (%)	38 (7.2)	37 (6.7)	50 (9.2)	29 (5.3)	0.09
Family history of premature CHD, number (%)	7 (1.3)	13 (2.3)	15 (2.8)	25 (4.6)	0.01
Family history of stroke, number (%)					0.01
≥60 years	46 (8.7)	69 (12.4)	69 (12.7)	78 (14.3)	
<60 years	14 (2.6)	23 (4.1)	18 (3.3)	32 (5.9)	
Hypertension, number (%)	339 (64.0)	398 (71.7)	389 (71.5)	374 (68.4)	0.02
Diabetes, number (%)	123 (23.2)	167 (30.1)	199 (36.6)	217 (39.7)	< 0.001

Values are expressed as mean ± standard deviation, unless noted otherwise.

TG, triglyceride; BMI, body mass index; SBP, systolic blood pressure; TIA, transient ischemic attack; CHD, coronary heart disease; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; TOAST, Trial of ORG 10172 in acute stroke treatment; LAA, large artery atherosclerosis; SVO, small-vessel occlusion; HbA1c, glycated hemoglobin; FTG, fasting triglycerides; NFTG, non-fasting triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aSampling interval time was calculated as the time interval between the last meal and sampling for lipid profiles.

	< 87 mg/dL (n = 530)	87–130 mg/dL (n = 555)	130–197 mg/dL (n = 544)	≥ 197 mg/dL (n = 547)	p- value
Hypercholesterolemia, number (%)	147 (27.7)	172 (31.0)	186 (34.2)	190 (34.7)	0.051
Atrial fibrillation, number (%)	191 (36.0)	138 (24.9)	108 (19.9)	83 (15.2)	< 0.001
Ever-smoking, number (%)	197 (37.2)	226 (40.7)	247 (45.4)	287 (52.5)	< 0.001
History of statin use, number (%)	122 (23.0)	147 (26.5)	114 (21.0)	111 (20.3)	0.06
Stroke profile					
NIHSS at admission, median (IQR)	4 (2– 12)	4 (2–9)	3 (1–8)	3 (1–6)	< 0.001
TOAST classification, number (%)					< 0.001
LAA	151 (28.5)	191 (34.4)	203 (37.3)	204 (37.3)	
SVO	60 (11.3)	89 (16.0)	99 (18.2)	123 (22.5)	
Cardioembolism	192 (36.2)	156 (28.1)	105 (19.3)	90 (16.5)	
Other determined	20 (3.8)	10 (1.8)	18 (3.3)	9 (1.6)	
Undetermined	107 (20.2)	109 (19.6)	119 (21.9)	121 (22.1)	
Laboratory findings					
HbA1c (%)	5.9 ± 1.1	6.2 ± 1.2	6.5 ± 1.4	6.7 ± 1.5	< 0.001
Fasting state					

Values are expressed as mean ± standard deviation, unless noted otherwise.

TG, triglyceride; BMI, body mass index; SBP, systolic blood pressure; TIA, transient ischemic attack; CHD, coronary heart disease; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; TOAST, Trial of ORG 10172 in acute stroke treatment; LAA, large artery atherosclerosis; SVO, small-vessel occlusion; HbA1c, glycated hemoglobin; FTG, fasting triglycerides; NFTG, non-fasting triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aSampling interval time was calculated as the time interval between the last meal and sampling for lipid profiles.

	< 87 mg/dL (n = 530)	87–130 mg/dL (n = 555)	130–197 mg/dL (n = 544)	≥ 197 mg/dL (n = 547)	p- value
Glucose (mg/dL)	103.2 ± 33.5	107.1 ± 40.0	113.4 ± 58.7	122.3 ± 50.7	< 0.001
Total cholesterol (mg/dL)	156.1 ± 35.9	166.1 ± 37.6	175.7 ± 41.0	186.8 ± 42.0	< 0.001
FTG (mg/dL)	64.9 ± 24.9	92.9 ± 37.8	123.2 ± 45.5	201.0 ± 106.8	< 0.001
HDL (mg/dL)	47.8 ± 12.9	44.7 ± 12.2	42.7 ± 12.1	39.9 ± 10.2	< 0.001
LDL (mg/dL)	90.6 ± 30.6	101.2 ± 32.1	109.6 ± 36.2	112.9 ± 36.2	< 0.001
Non-fasting state					
Glucose (mg/dL)	126.0 ± 48.2	131.1 ± 48.8	139.5 ± 66.7	149.2 ± 70.5	< 0.001
Total cholesterol (mg/dL)	167.3 ± 39.1	180.5 ± 41.2	191.8 ± 46.6	205.1 ± 44.4	< 0.001
NFTG (mg/dL)	63.9 ± 15.5	107.1 ± 12.6	159.0 ± 18.7	308.1 ± 135.8	< 0.001
HDL (mg/dL)	52.9 ± 16.5	50.0 ± 18.2	47.4 ± 18.2	44.2 ± 17.7	< 0.001
LDL (mg/dL)	96.1 ± 32.7	106.3 ± 36.3	115.0 ± 42.2	115.5 ± 39.6	< 0.001
Sampling interval time (min) ^a	252.1 ± 118.0	247.5 ± 114.5	248.3 ± 111.1	259.4 ± 107.1	0.28
Values are expressed as mean ± standard deviation, unless noted otherwise.					
TG, triglyceride; BMI, body mass index; SBP, systolic blood pressure; TIA, transient ischemic attack; CHD, coronary heart disease; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; TOAST, Trial of ORG 10172 in acute stroke treatment; LAA, large artery atherosclerosis; SVO, small-vessel occlusion; HbA1c, glycated hemoglobin; FTG, fasting triglycerides; NFTG, non-fasting triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.					
^a Sampling interval time was calculated as the time interval between the last meal and sampling for lipid profiles.					

The prevalence of fasting and non-fasting hypertriglyceridemia (≥ 200 mg/dL) was 11.5% (n = 251) and 24.6% (n = 536), respectively. Multivariate analysis revealed that age, BMI, initial SBP, and diabetes were independently associated with both fasting and non-fasting hypertriglyceridemia; hypercholesterolemia

and ever-smoking were associated with fasting hypertriglyceridemia; and family history of premature CHD and history of stroke or TIA were associated with non-fasting hypertriglyceridemia ($p < 0.05$) (Table 2). However, tests for examining the equality of ORs for each variable showed no inequality in the analyzed variables.

Table 2
Multivariate analyses and tests for equality of odds ratios for fasting and non-fasting hypertriglyceridemia (defined as triglycerides \geq 200 mg/dL)

	Fasting hypertriglyceridemia			Non-fasting hypertriglyceridemia			<i>p</i> -value for OR equality
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value	
Male sex	0.87	0.60–1.25	0.44	1.20	0.92–1.57	0.19	0.05
Age, 10 years	0.98	0.97–0.99	0.001	0.98	0.98–0.99	0.001	0.39
BMI, 1 kg/m ²	1.10	1.06–1.14	< 0.001	1.11	1.07–1.14	< 0.001	0.75
SBP, 10 mmHg	1.07	1.02–1.13	0.003	1.06	1.02–1.11	0.003	0.68
Family history of premature CHD	1.45	0.70–2.98	0.31	1.98	1.11–3.53	0.02	0.37
Family history of stroke							0.37
None	Reference			Reference			
\geq 60 years	1.29	0.86–1.92	0.22	1.34	0.99–1.82	0.06	
<60 years	0.88	0.46–1.67	0.70	1.34	0.81–2.23	0.25	
Medical history							
Stroke or TIA	0.84	0.57–1.22	0.35	0.67	0.50–0.90	0.01	0.22
CHD	1.00	0.56–1.79	0.99	0.66	0.42–1.03	0.07	0.19
Hypertension	1.10	0.78–1.56	0.57	0.96	0.75–1.23	0.72	0.36
Diabetes	1.72	1.28–2.33	0.004	1.71	1.37–2.14	< 0.001	0.95
Hypercholesterolemia	1.55	1.09–2.19	0.01	1.24	0.94–1.65	0.13	0.20
Atrial fibrillation	0.98	0.52–1.85	0.96	0.75	0.51–1.11	0.16	0.36

OR, odds ratio; BMI, body mass index; SBP, systolic blood pressure; CHD, coronary heart disease; TIA, transient ischemic attack.

	Fasting hypertriglyceridemia			Non-fasting hypertriglyceridemia			<i>p</i> -value for OR equality
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value	
Ever-smoking	1.43	1.02–2.02	0.04	1.15	0.90–1.48	0.27	0.18
History of statin use	0.66	0.42–1.01	0.06	0.75	0.54–1.06	0.10	0.49
Sampling interval time (min)	1.02	0.95–1.10	0.51	1.04	0.98–1.10	0.19	0.71

OR, odds ratio; BMI, body mass index; SBP, systolic blood pressure; CHD, coronary heart disease; TIA, transient ischemic attack.

Compared to the lowest quartile of NFTG, the highest quartile was negatively associated with the composite outcome in the unadjusted analysis, but this association was not statistically significant after adjustments for age and sex (Fig. 2, Supplemental table 3). The FTG and NFTG quartiles were not associated with any outcome variables after adjustments for predetermined potential confounders (Fig. 2, Supplemental tables 3 and 4). Moreover, fasting and non-fasting hypertriglyceridemia were not associated with an increased risk of any clinical outcomes (Table 3).

Table 3
Hazard ratios (HR) according to fasting and non-fasting hypertriglyceridemia^a

	Stroke recurrence		Composite outcome ^b	
	Crude HR (95% CI)	Adjusted HR ^c (95% CI)	Crude HR (95% CI)	Adjusted HR ^c (95% CI)
Fasting hypertriglyceridemia	0.96 (0.57–1.61)	1.24 (0.73–2.11)	0.61 (0.39–0.95)	0.92 (0.58–1.45)
Non-fasting hypertriglyceridemia	0.80 (0.53–1.20)	0.98 (0.65–1.49)	0.64 (0.47–0.87)	0.94 (0.68–1.30)

^aHypertriglyceridemia was defined as above 200 mg/dL

^bComposite outcome consisted of stroke recurrence, myocardial infarction and all kinds of death up to one year after onset.

^cAdjusted for age group, male sex, history of stroke or TIA, coronary heart disease, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, ever-smoking, statin use, initial NIHSS.

Discussion

This study found that (1) fasting and non-fasting lipid concentrations were well correlated; (2) fasting and non-fasting hypertriglyceridemia were prevalent in AIS patients; (3) fasting and non-fasting hypertriglyceridemia were associated with younger age, diabetes, and higher BMI and initial SBP; and (4) FTG and NFTG levels were not associated with the clinical outcomes.

Following food ingestion, TG is transported from the small intestines by chylomicrons through the bloodstream. Lipolysis of TG within chylomicrons, catalyzed by lipoprotein lipase, transforms these particles into atherogenic TG-remnant lipoproteins. Elevated postprandial TG levels, reflecting either higher peak levels or delay in clearance of TG-rich particles, can lead to accumulation of these atherogenic particles.¹³ The data presented in Supplement Table 1 corresponds to the expected time course of postprandial TG metabolism. In response to food intake, TG concentrations typically reach their peaks approximately 4 h after meals and decline thereafter.¹⁴ Thus, postprandial TG levels are more physiologic and better associated with thrombogenic conditions, such as ischemic stroke. Furthermore, our study suggests that patients with elevated FTG and NFTG levels show similar characteristics. Therefore, NFTG can replace FTG in the diagnostic evaluation of patients with AIS.

Several biological mechanisms provide plausible explanations about the associations between high FTG and NFTG concentrations and young age, higher BMI, higher SBP, and diabetes, which are components of the metabolic syndrome. Hypertriglyceridemia is a feature of dyslipidemia seen in type 2 diabetes and metabolic syndrome, which may also include insulin resistance, abdominal obesity, and hypertension.¹⁰ Hyperinsulinemia leads to an increase in the production of very-low-density lipoprotein.¹⁵ Hyperglycemia also impairs removal of TG-rich lipoproteins from circulation. Patients with poorly controlled diabetes have higher TG levels than those with well-controlled diabetes. Postprandial hyperlipidemia in diabetic patients appears to be prolonged, indicating that the arteries are exposed to atherogenic particles for extended periods.^{15,16}

In this study, both fasting and non-fasting TG levels were not associated with the composite outcome comprising of stroke recurrence, myocardial infarction, or all-cause mortality up to one year after the index stroke. Contradicting our results, in patients with established cardiovascular disease or risk factors, higher TG levels were reportedly associated with an increased risk of recurrent vascular events¹⁷, and reducing TG levels lowered the risk of ischemic events¹⁸. There are some explanations for these discrepancies. First, it has been reported that high TG levels might be associated with milder stroke severity and better outcomes in patients with AIS.^{19–21} In our study, NFTG negatively correlated with the initial National Institutes of Health Stroke Scale scores (Pearson correlation coefficient = - 1.33, $p < 0.001$). Second, TG could paradoxically prevent lipotoxicity, and subsequently poor outcome.^{22,23} Third, treatment with statin at discharge might attenuate the effect of high TG on outcome. The proportion of patients treated with statin at discharge was 88.5% in our study. In a previous study that reported a significant correlation between TG and recurrent stroke, the statin prescription rate was 36%.²⁴

Our study had several limitations. First, it only included Korean patients, and these results may not be generalizable to other populations. Second, the proportion of patients excluded from the analysis was 63%, accounting for a fairly large proportion. Particularly, when compared to patients excluded from this study, the proportion of young males, BMI, and prevalence of hyperlipidemia was relatively higher among the included patients, but the prevalence of diabetes did not differ between them (Supplemental table 5). The possibility of selection bias cannot be excluded, but the differences seemed considerably small to affect the clinical outcomes. Third, we did not have information on other possible factors affecting the lipid levels, such as foods, drugs, and nutritional state.

Conclusion

In conclusion, our study shows that AIS patients with fasting and non-fasting hypertriglyceridemia may not differ in their clinical characteristics and outcomes. Furthermore, fasting and non-fasting TG levels were not associated with subsequent clinical events, including stroke recurrence, myocardial infarction, and all-cause mortality up to one year.

Declarations

Acknowledgements

None

Author contributions

J.Y. Kim: Participated in literature search, study design, data collection, analysis, interpretation, and writing the manuscript which was then developed further in collaboration with the other authors. M-S Kye, K-J Lee, J. Kang, B.J. Kim, M-K Han, K. Kang, J-M Park, T.H. Park, H-K Park, Y-J Cho, K-S Hong, K.B. Lee, M.S. Jang: Participated in the study design, data collection, and revision of the manuscript. J.S. Lee, J. Lee: Primarily active in statistical methodology and data interpretation, but also in manuscript writing in collaboration. H-J Bae: Participated in study design, data collection and interpretation. Revised the manuscript and approved the final version. All authors gave final approval of the manuscript.

Competing interests

H-J Bae is the principal investigator. He is also a member of the steering committee, and/or a site investigator of multicenter clinical trials or clinical studies that are sponsored by BMS Korea, Shinpoong Pharm. Co. Ltd., Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Esai, AstraZeneca Korea, Servier Korea, Yuhan Corporation, Jeil Pharmaceutical Co., Shire Korea, JLK inspection, Chong Gun Dang Pharmaceutical Corp., and Dong-A Pharmaceutical. He has received lecture honoraria from Esai, Shire Korea, Amgen, and Otsuka Korea outside of this work. The other authors declare no competing interests.

This research was partially supported by the research fund of the Korea Centers for Disease Control and Prevention (2020ER620200#) and Daewoong Pharmaceutical Co. Ltd. The funding sources had no role in the study design, data collection, analysis and interpretation, as well as preparation, review, and approval of the manuscript.

References

1. Nordestgaard, B. G. & Varbo, A. Triglycerides and cardiovascular disease., **384**, 626–635 [https://doi.org/10.1016/S0140-6736\(14\)61177-6](https://doi.org/10.1016/S0140-6736(14)61177-6) (2014).
2. Cohn, J. S., McNamara, J. R., Cohn, S. D., Ordovas, J. M. & Schaefer, E. J. Postprandial plasma lipoprotein changes in human subjects of different ages. *J Lipid Res*, **29**, 469–479 (1988).
3. Schaefer, E. J. *et al.* Comparison of fasting and postprandial plasma lipoproteins in subjects with and without coronary heart disease. *Am J Cardiol*, **88**, 1129–1133 (2001).
4. Bansal, S. *et al.* Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*, **298**, 309–316 <https://doi.org/10.1001/jama.298.3.309> (2007).
5. Nordestgaard, B. G., Benn, M., Schnohr, P. & Tybjaerg-Hansen, A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*, **298**, 299–308 <https://doi.org/10.1001/jama.298.3.299> (2007).
6. Langsted, A., Freiberg, J. J. & Nordestgaard, B. G. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction., **118**, 2047–2056 <https://doi.org/10.1161/CIRCULATIONAHA.108.804146> (2008).
7. Kim, B. J. *et al.* Current status of acute stroke management in Korea: a report on a multicenter, comprehensive acute stroke registry. *Int J Stroke*, **9**, 514–518 <https://doi.org/10.1111/ijvs.12199> (2014).
8. Kim, B. J. *et al.* Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. *J Stroke*, **17**, 38–53 <https://doi.org/10.5853/jos.2015.17.1.38> (2015).
9. Adams, H. P. Jr. *et al.* Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and : The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation* **115**, e478-534, doi:10.1161/CIRCULATIONAHA.107.181486 (2007).
10. Expert Panel on Detection. E. & Treatment of High Blood Cholesterol in, A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*, **285**, 2486–2497 (2001).
11. Gauvreau, K. & Pagano, M. The Analysis of Correlated Binary Outcomes Using Multivariate Logistic Regression. *Biom. J*, **39**, 309–325 <https://doi.org/10.1002/bimj.4710390306> (1997).

12. Ko, Y. *et al.* MRI-based Algorithm for Acute Ischemic Stroke Subtype Classification. *J Stroke*, **16**, 161–172 <https://doi.org/10.5853/jos.2014.16.3.161> (2014).
13. Ginsberg, H. N. New perspectives on atherogenesis: role of abnormal triglyceride-rich lipoprotein metabolism., **106**, 2137–2142 (2002).
14. Boquist, S. *et al.* Alimentary lipemia, postprandial triglyceride-rich lipoproteins, and common carotid intima-media thickness in healthy, middle-aged men., **100**, 723–728 (1999).
15. Coughlan, B. J. & Sorrentino, M. J. Does hypertriglyceridemia increase risk for CAD? Growing evidence suggests it plays a role. *Postgrad Med*, **108**, 77–84 <https://doi.org/10.3810/pgm.2000.12.1314> (2000).
16. Kreisberg, R. A. Diabetic dyslipidemia. *Am J Cardio* **82**, 67U-73U; discussion 85U-86U (1998).
17. van de Woestijne, A. P. *et al.* Plasma triglyceride levels increase the risk for recurrent vascular events independent of LDL-cholesterol or nonHDL-cholesterol. *Int J Cardiol*, **167**, 403–408 <https://doi.org/10.1016/j.ijcard.2012.01.008> (2013).
18. Bhatt, D. L. *et al.* Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med*, **380**, 11–22 <https://doi.org/10.1056/NEJMoa1812792> (2019).
19. Pikija, S. *et al.* Higher serum triglyceride level in patients with acute ischemic stroke is associated with lower infarct volume on CT brain scans. *Eur Neurol*, **55**, 89–92 <https://doi.org/10.1159/000092780> (2006).
20. Weir, C. J., Sattar, N., Walters, M. R. & Lees, K. R. Low triglyceride, not low cholesterol concentration, independently predicts poor outcome following acute stroke. *Cerebrovasc Dis*, **16**, 76–82 <https://doi.org/10.1159/000070119> (2003).
21. Dziedzic, T., Slowik, A., Gryz, E. A. & Szczudlik, A. Lower serum triglyceride level is associated with increased stroke severity., **35**, e151–152 <https://doi.org/10.1161/01.STR.0000128705.63891.67> (2004).
22. Eun, M. Y. *et al.* Age-dependent predictors for recurrent stroke: the paradoxical role of triglycerides. *Eur Neurol*, **69**, 171–178 <https://doi.org/10.1159/000345480> (2013).
23. Listenberger, L. L. *et al.* Triglyceride accumulation protects against fatty acid-induced lipotoxicity. *Proc Natl Acad Sci U S A*, **100**, 3077–3082 <https://doi.org/10.1073/pnas.0630588100> (2003).
24. Zhao, L. *et al.* Association between atherogenic dyslipidemia and recurrent stroke risk in patients with different subtypes of ischemic stroke. *International Journal of Stroke*, **10**, 752–758 (2015).

Figures

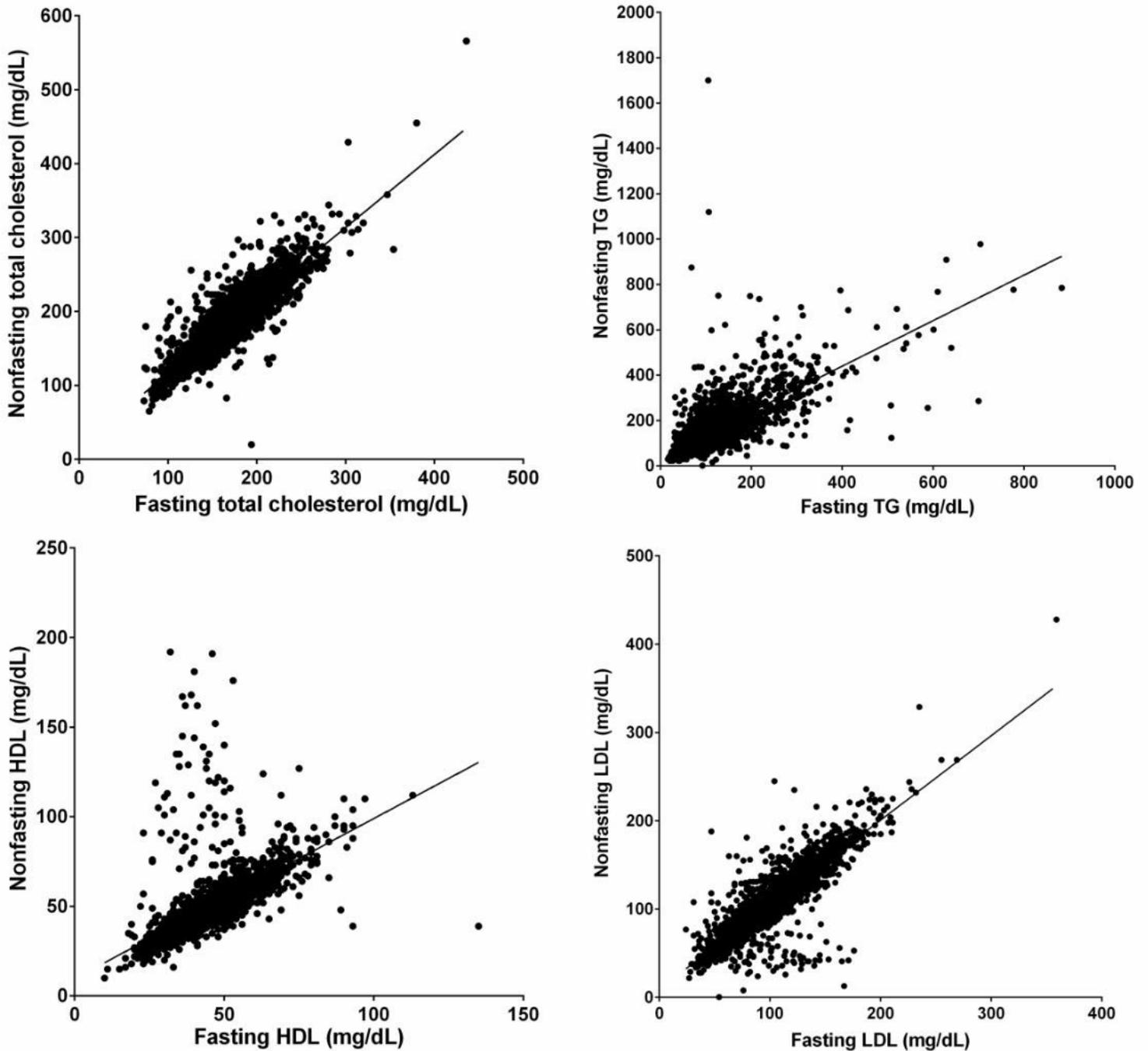


Figure 1

Correlation analyses between fasting and non-fasting lipid profiles. Fasting and non-fasting lipid profiles were well correlated for total cholesterol, TG, HDL, and LDL. Pearson's correlation coefficients were 0.88 for total cholesterol, 0.70 for TG, 0.60 for HDL, and 0.85 for LDL ($p < 0.001$ for all). (TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein)

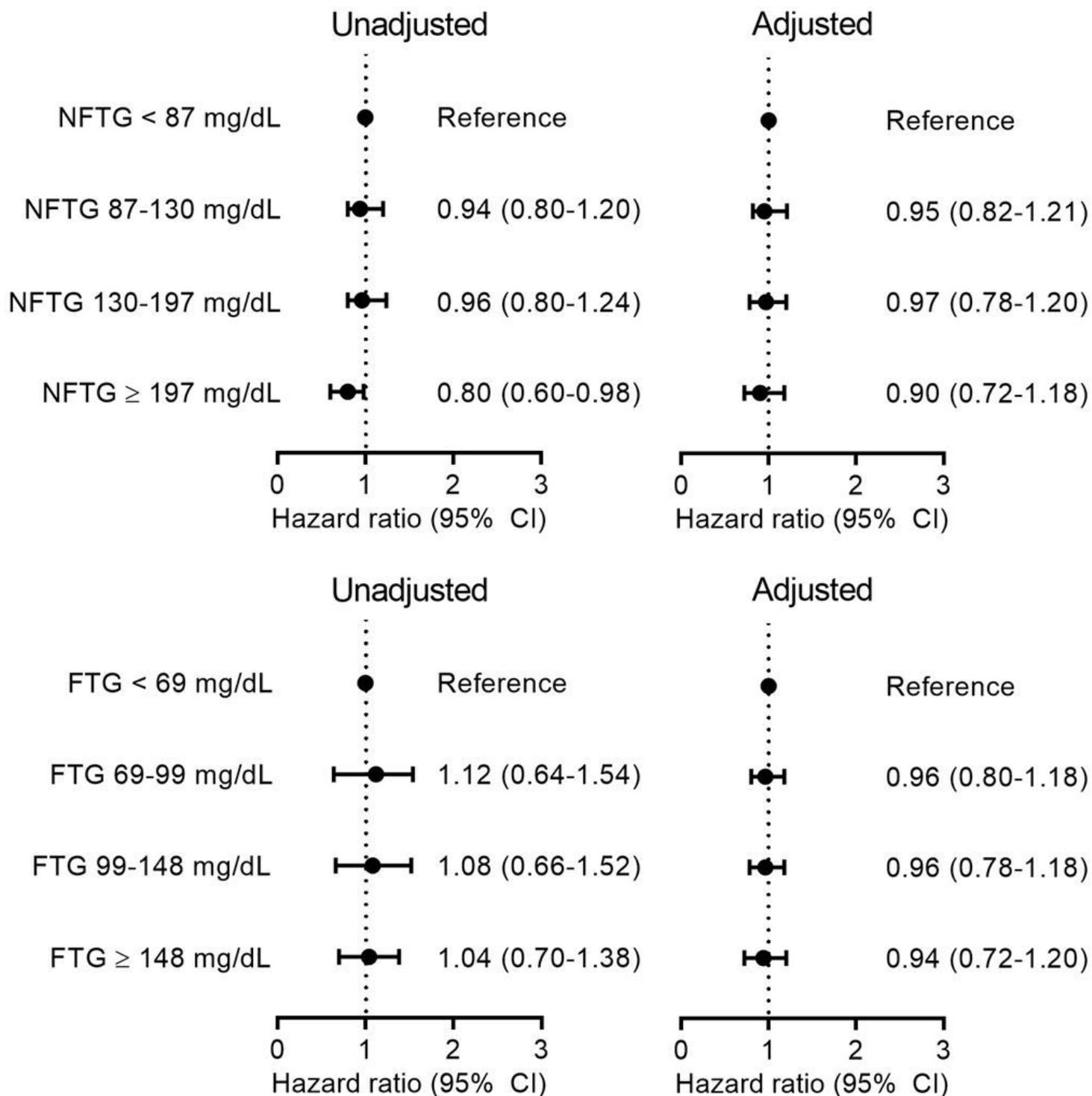


Figure 2

Cox's proportional hazard model according to the quartiles of fasting and non-fasting triglycerides for the composite outcome Hazard ratios were adjusted for age, sex, history of stroke or transient ischemic attack, history of coronary heart disease, hypertension, diabetes mellitus, atrial fibrillation, ever-smoking, history of statin use, and Trial of Org 10172 in acute stroke treatment classification. The composite outcome consisted of stroke recurrence, myocardial infarction, and all-cause mortality up to one year after the index stroke. (CI, confidence interval; NFTG, non-fasting triglycerides; FTG, fasting triglycerides)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementalmaterials.docx](#)